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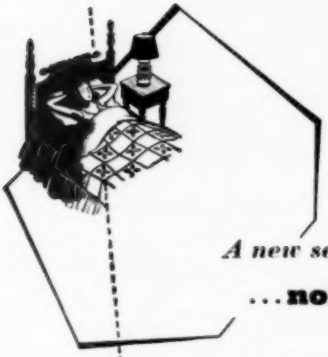

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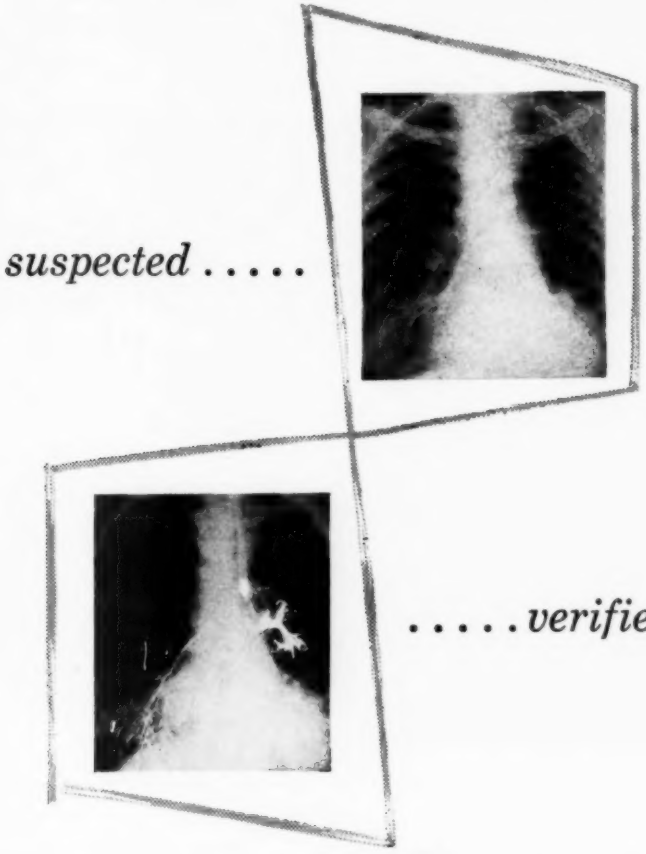

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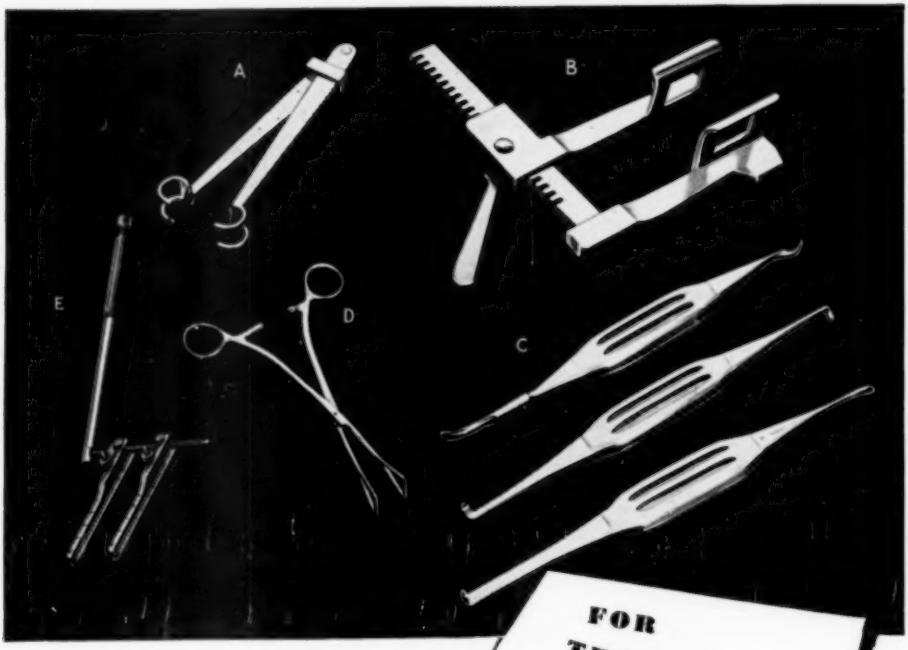

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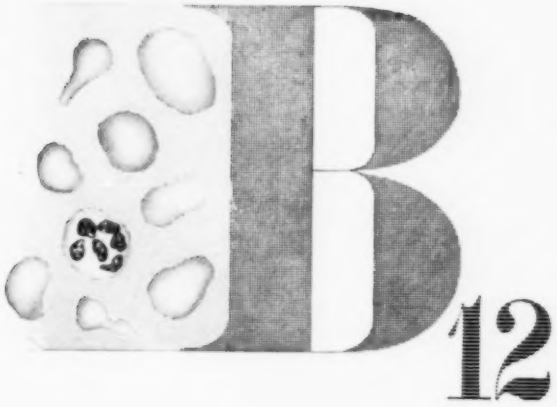

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EMPYEMA AS A COMPLICATION OF CHRONIC PULMONARY TUBERCULOSIS

OSCAR AUERBACH[1,2]

(Received for publication January 17, 1949)

Empyema as a frequent complication of chronic pulmonary tuberculosis is in many of its aspects poorly understood. In an effort to clarify some of the controversial points, it was decided to review all of the cases of empyema which came to autopsy. An attempt was made to correlate such factors as treatment with pneumothorax, bronchopleural fistulas, and bacteriologic findings with the development and course of empyema.

COMPOSITION OF SERIES

One thousand eight hundred seventy-four consecutive autopsies of chronic pulmonary tuberculosis were reviewed. Among these there were 311 cases of empyema, an incidence of 16 per cent.

Diagnostic criteria: All cases in which purulent material was present in the pleural cavity were included in this series. No distinction was made in this study between gradations of the pus as to consistency, specific gravity, or bacteriological variants within the fluid.

Age: The youngest person in the series was 8 years of age, while the oldest was 70 years of age. From table 1 it may be seen that the majority of cases occurred in the age period between 20 and 40 years, the age period in which the greatest number of cases of chronic pulmonary tuberculosis is observed at autopsy.

Sex: There were 205 men and 106 women. This was in direct proportion of men to women in the general autopsies during this period.

Color: One hundred and ninety-one (61.09 per cent) were white, 118 (37.9 per cent) were Negroes, while two (0.6 per cent) were of the Asiatic race. This is also directly proportional to the color distribution in the general autopsy series.

Artificial Pneumothorax

Two hundred and fifty-two (81 per cent) of cases of empyema occurred in the presence of an artificial pneumothorax on the same side, while fifty-nine (19 per cent) were found in cases without antecedent treatment.

Duration of chronic pulmonary tuberculosis before induction of artificial pneumothorax: In table 2 it may be seen that 110 cases (42 per cent) in the series were those in which pneumothorax had been started one to three months after the onset of chronic pulmonary tuberculosis. Another 70 occurred in patients in whom pneumothorax had been started between the fourth and seventh months

[1] Laboratory service, Halloran VA Hospital, Staten Island 2, New York.

[2] This material was gathered while the author was at Sea View Hospital, Staten Island, New York.

after the onset of the disease. In the remaining 72 cases (28 per cent), the pneumothorax was begun from eight months to sixteen years after the onset of the disease.

Duration of artificial pneumothorax: It may be seen in table 3 that the pneumothoraces in the series were maintained from one month to five years before abandonment. Occasionally pneumothorax was abandoned because the collapse was considered as inadequate, the empyema subsequently developing in the patent pleural space. In some instances collapse therapy was interrupted because of clinical signs of a bronchopleural fistula. In the vast majority of cases, however, the reason for the abandonment of the artificial pneumothorax was the appearance of purulent fluid in the pleural cavity.

TABLE 1

Age Distribution

(311 cases of empyema complicating pulmonary tuberculosis)

	AGE							
	1 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70
Number of Cases.....	1	19	116	93	50	25	6	1

TABLE 2

Duration of Chronic Pulmonary Tuberculosis before Induction of Artificial Pneumothorax

NUMBER OF MONTHS	NUMBER OF CASES	NUMBER OF MONTHS	NUMBER OF CASES
1	49	26	2
2	30	27	2
3	31	28	2
4	18	29	1
5	20	30	1
6	16	31	1
7	16	32	0
8	3	33	1
9	6	34	2
10	4	35	0
11	8	36	2
12	4	37	0
13	2	38	1
14	5	39	1
15	1	40	0
16	1	41	0
17	1	42	1
18	1	43	0
19	0	44	1
20	1	45	0
21	0	46	0
22	1	47	1
23	0	48	1
24	0	49 to 282	13
25	1		

In 150 cases (59.5 per cent) the pneumothorax was abandoned from one to eight months after the initial induction. In 55 instances (21.8 per cent) collapse therapy was abandoned from nine to eighteen months after it was started. In the remaining 47 cases (18.7 per cent) it was given up from nineteen months to five years later.

When the pneumothorax had been maintained for a long period of time before the development of the empyema, the bronchopleural fistula, when found, was at the base of a chronic cavity in the upper lobe of the lung (figure 4b).

TABLE 3

Duration of Artificial Pneumothorax

NUMBER OF MONTHS	NUMBER OF CASES
1	30
2	23
3	18
4	22
5	15
6	13
7	14
8	15
9	4
10	5
11	9
12	10
13	4
14	8
15	3
16	3
17	3
18	6
19 to 60	47

From this study it seems justifiable to state that in cases of artificial pneumothorax empyema is an early complication of the therapy, but may occur so long as the collapse is maintained in the presence of an open cavity.

PATHOLOGIC ANATOMY

In the vast majority of cases the empyema cavity was located in the lateral aspect of the chest. It usually extended from the inferior aspect of the upper lobe to the base of the lower lobe. The cavity extended for a variable distance toward the anteromedian and also toward the posteromedian aspects of the chest. In all regions the boundary of the empyema cavity was the fused visceral and parietal layers of the pleura. In most instances the empyema cavity measured about 15 cm. in the apico-basal direction and 12 cm. in width. There were variations in the size and position of the empyema space. In some cases the empyema cavity continued for a variable extent along the diaphragmatic surface. Less frequently it extended toward the apical aspect of the lung. In a

few cases the empyema cavity measured from 3 to 4 cm. and was localized over a bronchopleural fistula. Occasionally the empyema cavity was present in the medial aspect, usually associated with a bronchopleural fistula in the right middle lobe.

The amount of pus within the pleural cavity at the time of the autopsy varied greatly (100 cc. to 3 L.) and depended to a great extent upon how much fluid had been withdrawn just prior to death. The pus was thick in some instances; thin in others. The color varied from grey to green and sometimes had a red tinge due to blood.

The wall of the empyema cavity in early cases was thin, measuring less than one mm. in thickness. It was formed by the slightly thickened visceral and parietal pleurae. The pleural surfaces were lusterless and revealed small amounts of attached fibrin. The fluid in the pleural cavity was small in amount, thin, and contained fibrin.

In the more protracted cases the pleurae were thicker, the process being more marked in the parietal layer. The inner surfaces were lined by a thicker layer of fibrin. Beyond this there was a narrow red zone of vascular granulation tissue. These cavities contained larger amounts of pleural fluid which was thicker in consistency (figure 6).

In the oldest cases the pleurae were still thicker and in advanced cases reach a thickness of 2 to 3 cm. in the parietal aspect and one to 2 cm. in the visceral aspect. The increased thickness was due to a progressive increase of the grey-white fibrous zone beyond the red zone of granulation tissue. It is of interest that in the visceral aspect this grey zone was not always an intimate part of the visceral pleura but was attached to the latter by a thin membrane. Thus, in those cases in which there has been a complete closure of a bronchopleural fistula and an anatomic healing of the tuberculous process within the lung, i.e., closure of the cavities and conversion of the sputum to "negative", a pleurectomy is possible and indicated. Re-expansion of the underlying lung is possible if the pulmonary tuberculous process has caused no excessive destruction and fibrosis of the lung.

The thickened parietal pleura was intimately adherent to the overlying endothoracic fascia and the soft tissue of the chest wall. The pleura was so firmly connected with the overlying tissue that it could be removed from the chest cavity only with great difficulty. The greater portion of the parietal pleura was grey-white connective tissue, but in its outer portions fat might be found. Removal of the pleura from the chest wall was usually difficult, since there is no plane of cleavage. The outer surface of the pleura was attached to muscle. The pleura was often of cartilaginous consistency and contained deep grooves underlying the sites of the ribs (figure 4a).

Bronchopleural Fistulas

Bronchopleural fistulas were present in 153 cases in the series (49.1 per cent). In 112 cases there were single openings and 41 cases with multiple fistulas.

Where multiple perforations were present, they were located either in different lobes on the same side or in the same lobe. The size of the fistulas varied from less than one mm. to that of almost an entire lobe; the latter having occurred

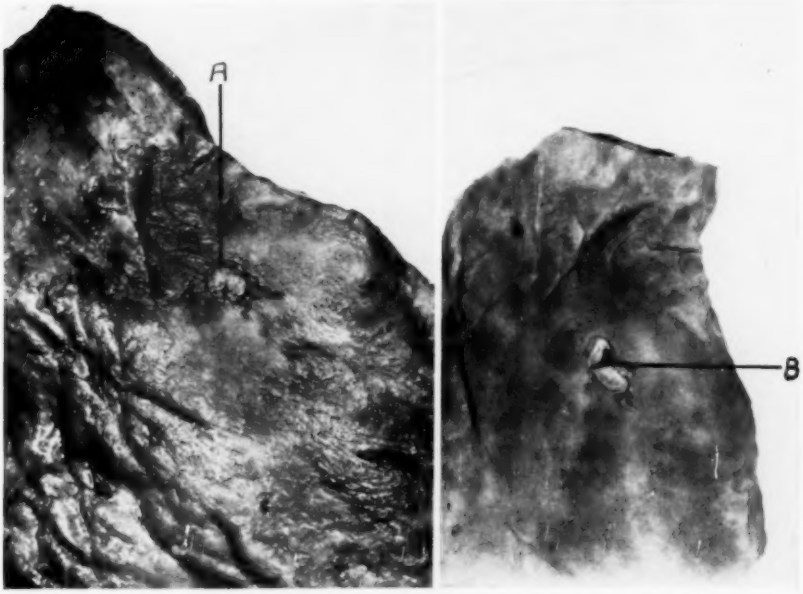

FIG. 1a. (Left) The visceral pleura over the right lung of a 29 year old man who had been receiving artificial pneumothorax on the right side for one month before his death. The total duration of his disease was sixteen months. The patient expired two days after definite clinical signs of a spontaneous pneumothorax on the right side. After diligent search a cap of fibrinous tissue (a) was found firmly attached to the visceral pleura.

FIG. 1b. (Right) Removal of the fibrinous cap in figure 1a (b) revealed a 2 mm. opening in the visceral pleura which communicated with a large cavity in the upper lobe of the right lung.

where artificial pneumothorax was instituted in cases of extensive caseous lobular pneumonia (figures 2a and 2b). The distribution was as follows:

Upper lobe of the left lung	52
Lower lobe of the left lung	19
Both lobes of the left lung	8
Upper lobe of the right lung	44
Middle lobe of the right lung	4
Lower lobe of the right lung	16
Upper and lower lobes of right lung	8
Middle and lower lobes of right lung	2

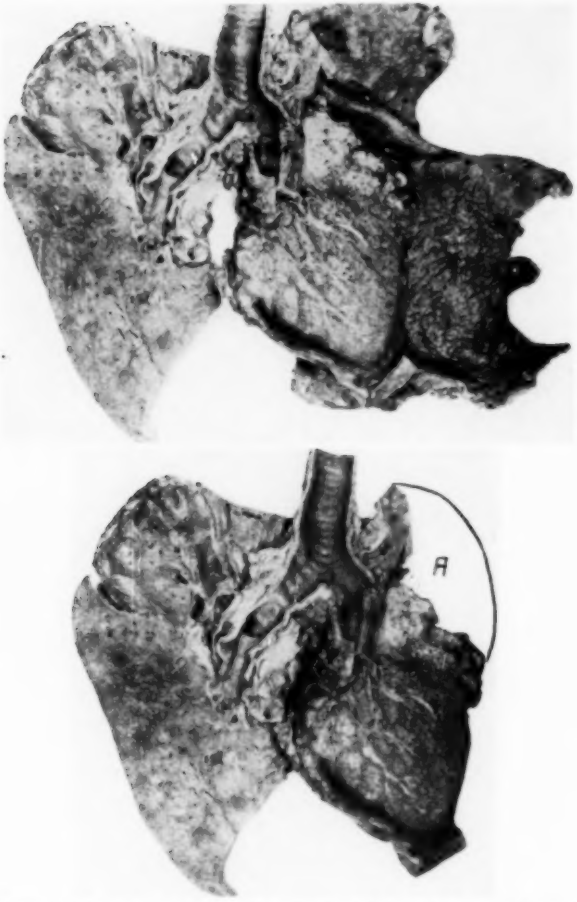

FIG. 2a. (Upper) A large empyema cavity on the left in a 32 year old man whose total duration of illness was seven months. An artificial pneumothorax was begun three and one-half months after the onset of the disease. The parietal pleura is slightly thickened and lined by a grey granular surface. A confluent caseous lobular pneumonia is present throughout both lungs. Tubercle bacilli and staphylococci were found in the pleural fluid during life and *B. pyocyaneus* were recovered after a thoracotomy was performed.

FIG. 2b. (Lower) The same view as figure 2a with the parietal pleura removed. The greater part of the upper lobe of the right lung (a) has been excavated into the pleural cavity. The black line indicates the former border of the lung parenchyma.

Microscopic Appearance

The morphologic appearance of the inflammatory process was a uniform one in all cases, and the same in cases where the bacteriologic studies showed pyogenic organisms or tubercle bacilli as in those in which no organisms were found

in the pleural exudate during life. The presence of a zone of caseation lining the pleural surfaces in the last group would indicate that the pleural fluid had not been sterile.

The inner aspect of the pleura in the early cases was lined in part by a variably wide pink granular zone of caseation and in part by a zone of fibrin containing polymorphonuclear leukocytes and nuclear debris. Toward the periphery of this zone were fibroblasts and epithelioid cells. A narrow to wide zone of vascular granulation tissue surrounded the inner layer. This was composed of fibro-

FIG. 3. A coronal section of the upper lobe of the right lung of a 29 year old Negro woman whose total duration of illness was twenty-one months. An artificial pneumothorax on the right side was begun seventeen months after the onset of her disease. A Jacobeus operation to sever an adhesion was performed three weeks before her death. A portion of the severed band is still present, but most of it has sloughed away. A bronchopleural fistula is located at the site of the adhesion band.

blasts, epithelioid cells, Langhans' giant cells, dilated capillaries, and collagen fibrils. In some areas the cellular elements were arranged to form tubercles. Tubercle formation and giant cells were generally not as frequently found as in the tuberculous granulation tissue in the lung parenchyma. It was often necessary to examine multiple sections of the pleura to establish the tuberculous character of the process with certainty.

Beyond the granulation tissue was a zone of loose connective tissue, wider in the parietal than the visceral aspects, which became progressively thicker as the process continued.

Bacteriology

Some classifications (1, 2, 3) of empyema contain two groups and are so divided according to the bacteriologic findings of the fluid. One group is tuberculous

FIG. 4a. (Top) A large empyema cavity on the right in a 26 year old woman whose total duration of illness was forty-four months. An artificial pneumothorax on the right side was begun six months after the onset of her illness and abandoned thirty-one months later because of fluid in the pleural space. The greatly thickened parietal pleura (a) is adherent to the muscles of the chest wall. An adhesion band (b) is present between the visceral and parietal pleurae. The opening of a bronchopleural fistula is seen in the visceral pleura (c).

FIG. 4b. (Bottom) A coronal section of the right lung (figure 4a) shows it to be greatly compressed. A probe is seen passing through the cavity and the opening in the visceral pleura. Only tubercle bacilli were recovered from the pleural fluid during life.

empyema in which only tubercle bacilli are recovered, and the other mixed infection empyema in which in addition pyogenic organisms are also found.

In the present series, bacteriological examination of the pleural fluid was not performed in 101 cases. In the 210 cases in which a study of the fluid was made, 89 showed the presence of tubercle bacilli in pure culture while 78 contained tubercle bacilli and pyogenic organisms. In 19 cases only pyogenic organisms were found and in 24 cases the cultures were sterile.

FIG. 5. A greatly compressed lung on the left due to an empyema cavity in a 49 year old man whose total duration of illness was six years. An artificial pneumothorax on the left side was begun two and one-half years after the onset of disease. Death occurred during a second stage thoracoplasty (left) when the pus in the pleural cavity was aspirated into the right lung through a small bronchopleural fistula (a) in the lower lobe of the left lung. The compressed lung is resilient throughout its greater extent. The pleurae over the upper part of the lung are greatly thickened and the pleural space obliterated. Streptococci and tubercle bacilli were cultured from the pus during life.

Except for *M. tuberculosis*, staphylococci were most frequently found in the pleural cavity. This finding is in agreement with the observations reported in the literature. A few authors (4, 5, 6) have pointed out that the finding of staphylococci in an empyema in itself suggests that the condition may be primarily tuberculous. Less frequently isolated were pneumococci and streptococci.

In a small group of cases (35) three other organisms were found in the empyema cavity. These were *B. proteus*, *B. pyocyaneous* and in two instances, *E. coli*. It is interesting that in this group the organisms in all instances appeared after

a communication with the outside. The opening to the outside was the result of a thoracotomy nineteen times, an empyema necessitatis three times, and following a Schede operation, thirteen times.

Another feature of the bacteriologic studies is the great variation in the findings obtained from repeated studies of the purulent fluid removed from the same patient. The variations were great and in many instances extremely inconsistent. In some instances no organisms were recorded, other times tubercle bacilli, and at

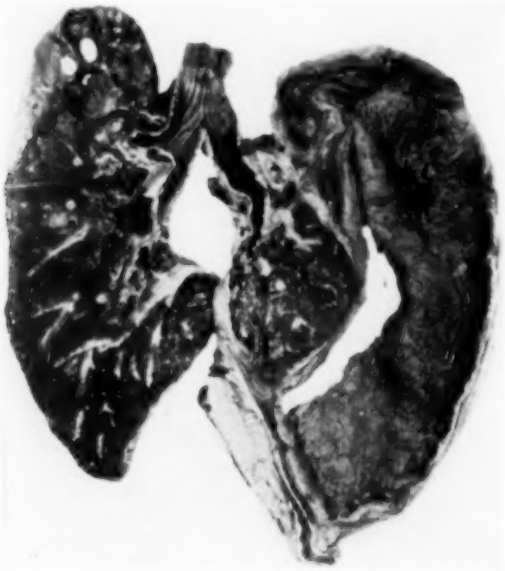

FIG. 6. A large empyema cavity on the left occurring in a 34 year old woman whose total duration of illness was twenty-three months. An artificial pneumothorax on the left side was begun five months after the onset of her disease. A bronchopleural fistula in the upper lobe of the left lung is not visualized in this view. The thickened parietal pleura is lined by a thick green "velvety" surface. An empyema necessitatis which had not ruptured through the skin was present in the left breast. Tubercle bacilli, but no pyogenic organisms, were cultured from the pus removed during life.

other times pyogenic organisms in association with tubercle bacilli. The pyogenic organisms, when recovered, were not always the same.

Healing of Pulmonary Cavities on Side of Empyema

In fifty (16 per cent) of the cases in this series the cavity in the lung had undergone anatomic healing either in the form of an inspissated cavity or a radial scar. In 24 instances cavities were present in the other lobes of the same lung or on the opposite side. In the remaining 26 cases the entire tuberculous process, including the cavity, was either in the stage of healing or was anatomically healed.

In 26 of the 50 cases, an artificial pneumothorax was performed to collapse the cavity and, although in these cases the object was accomplished, the complication resulting from the procedure was the direct or indirect cause of death in many instances. Some of the patients died in uremia secondary to amyloidosis and others of a bronchopneumonia following one of the operations to obliterate the empyema cavity.

Complications

Empyema necessitatis: There were 32 (9.7 per cent) cases in the series which showed evidence of an empyema necessitatis. This is considerably lower than the 24 per cent reported by Sindel (7) in a clinical study from this institution. The basis of this difference lies in the fact that most of the cases in the present series underwent extensive surgical treatment during life in the form of aspirations, thoracostomies, and thoracoplasties.

In all but four instances the empyemata occurred in cases treated with artificial pneumothorax.

In all but one case, the empyema necessitatis was present in the form of an abscess in the soft issue of the chest wall. In the one exception it perforated the esophagus and resulted in a pleuro-esophageal fistula.

The abscess in the chest wall, usually found in the anterolateral chest wall, communicated with the pleural empyema through one or more openings which varied in size from 2 mm. to 2 cm. The latter were enlarged needle tract openings lined by tuberculous granulation tissue. The chest wall abscess varied in size from 2 cm. to 5 cm. in diameter. In 22 of the cases the abscess ruptured through the skin to form a pleurocutaneous fistula.

Amyloidosis: In 107 (34 per cent) of the cases, amyloidosis of varying degrees was present. This compares with 22 per cent in the general autopsy series during this period of time and 35 per cent which were observed in skeletal tuberculosis.

Amyloidosis was present to a much greater extent in those cases in which the empyema had been present for long periods of time. There can be no question that empyema is an important predisposing factor in the development of amyloidosis.

The amyloid deposits were present chiefly in the liver, spleen, kidneys, and adrenal glands. In some of the cases the tuberculous process within the lungs underwent anatomic healing (with cavity closure) and the patient died of uremia, resulting from an extensive amyloidosis in the kidneys.

DISCUSSION

It has been our impression that the cause of the empyema in each instance is a bronchopleural fistula. The importance of bronchopleural fistula as an etiologic factor was recognized by Duboff (8) and stressed by Coryllos (9).

In many of the cases of empyema in the present series, in which there was no bronchopleural fistula present at the time of the autopsy, there was a definite episode which pointed to the presence of one during the patient's life. These episodes included: marked shifts of the mediastinum to the opposite side; the

rapid appearance of highly positive pleural pressures on the affected side; the expectoration of methylene blue when instilled into the pleural cavity; and shortness of breath and pain on the side of involvement.

Bronchopleural fistulas were present in 153 (49.1 per cent) in this series. Woodruff (10) reported an incidence of 30 per cent bronchopleural fistulas in his 154 cases of tuberculous empyema. The reason for his lower incidence lies in the fact that he included in his empyemas any fluid, whether purulent or not, which contained tubercle bacilli. On the other hand, the writer has never observed a case of bronchopleural fistula which had been present for a few days in which an empyema had not been present. It should be stressed that not all cases of spontaneous pneumothorax are followed by empyema. In non-pneumothorax treated cases rapid healing of the fistula with re-expansion of the lung may result in adhesion of the pleural surfaces and obliteration of the space. The writer is in agreement with Leaver and Hardaway (1) that whether or not a patient undergoing pneumothorax therapy develops an empyema depends upon the duration and size of the bronchopleural fistula.

There are cases of bronchopleural fistula which give none of the signs or symptoms just described. These have been designated as "silent", "latent", or "mute" bronchopleural fistulas. Vineberg and Aronowitch (11) believe that the frequent and often undetected presence of bronchopleural fistula in artificial pneumothorax accounts for the increase in empyema which has occurred in the past twenty-five years.

The question arises as to how one may reconcile the presence of so many cases of empyema in the absence of a bronchopleural fistula. The answer to this is that bronchopleural fistulas may heal and in fact do so frequently.

This process is best seen in small fistulas where the healing process is a rapid one. In such cases we have observed a serofibrinous exudate present around the periphery of the recent perforation. This exudate extends to cover the opening and is later transformed into fibrous tissue. At this stage of healing it is difficult and often impossible to find the site of perforation, despite the fact that there had been definite clinical evidence of its presence. Healed perforations cannot be distinguished from subpleural cavities with thickening of the overlying pleura. In a number of cases we were able to demonstrate this method of healing. These patients expired from two to four days after a spontaneous pneumothorax and at autopsy a 2 to 4 mm. fistulous opening was hidden and sealed by a fibrinous cap (figure 1a). Upon removal of the fibrin an open fistula was found (figure 1b). These sites were found with considerable difficulty even in this early stage of healing.

Pollock and Skinner (12) in their clinical observations of cases under artificial pneumothorax found that although the pleuropulmonary fistula is only of a temporary nature it exists sufficiently long to infect the pleural space with tubercle bacilli. Since it was their routine to do fluoroscopic examinations before and after pneumothorax refills, the detection of superimposed spontaneous pneumothorax was often made when unsuspected. Prior to refill they found the

lung compressed in excess to that observed at last fluoroscopy. This finding was soon followed by a pleural exudate.

The emptying of the contents of a pulmonary cavity or liquefied caseous focus into the pleural cavity through the perforation sets up an inflammatory process in the pleura. This inflammatory process, regardless of the type of bacteria involved, has a uniform gross and microscopic appearance. It is not unusual to isolate different species of bacteria from a given empyema cavity at different times.

The finding of pyogenic organisms in the pleural empyema is an extremely interesting feature as the presence of pyogenic organisms in the tuberculous cavity within the lung is a rare occurrence. Yet, in cases with a bronchopleural fistula without thoracotomy drainage, pyogenic organisms are found in the pleural space with great regularity. It is difficult to explain why the bacterial flora present in the bronchi do not gain access to the vomica in the lung, yet when this structure perforates into the pleural cavity, pyogenic organisms are found in the latter. Even in these latter cases, however, pyogenic organisms are rarely found in the pulmonary cavity. A study of the organisms in the empyema cavity (staphylococci, pneumococci, streptococci) indicates that they are the type found normally in the mouth.

The findings of the present study substantiate the often repeated statement that empyema in chronic pulmonary tuberculosis is chiefly (81 per cent of cases) a complication of artificial pneumothorax. It is interesting to note that Vineberg and Aronowitch (11) in their study also found 81 per cent of their empyema cases were secondary to induced pneumothorax. In 2 instances there was empyema present on both sides; both occurred in the presence of a bilateral artificial pneumothorax.

It is unfortunate that in the present series data are not available concerning number of patients with artificial pneumothorax who died during this period so that it would be possible to determine the incidence of empyema in cases of fatal chronic pulmonary tuberculosis with artificial pneumothorax. The incidence as reported by different men (1, 8, 11, 13–16) varies considerably, however, with a range from 5.8 to 40 per cent.

There are three main sources given for the infection: (*1*) rupture of a cavity or a subpleural caseous focus into the patent pleural space; (*2*) tearing of an adhesion; and (*3*) infection from without.

Rupture of a cavity or subpleural focus into the patent pleural spaces: The tuberculous process in the lung usually begins as an area of tuberculous pneumonia in the posterolateral portion of the upper lobe, usually about 2 or 3 cm. above the interlobar fissure. This site corresponds to the infraclavicular shadow observed in the roentgenograms. Surrounding the tuberculous pneumonia is a perifocal reaction the extent of which usually varies with the size of the focus it surrounds. This reaction extends to the pleura and results in a localized serofibrinous exudate. As the process continues the tuberculous pneumonia undergoes caseation, liquefaction, and cavity formation. With the development of caseation, a zone

of vascular granulation tissue develops around it and the perifocal reaction is organized into connective tissue to form the outer wall of the cavity. The perifocal reaction in the pleura is organized into connective tissue so that localized adhesions are formed in the region of the cavity. In later stages this may serve as a protective barrier to the spread of the disease.

If artificial pneumothorax is instituted during the stage of progression, *i.e.*, in the first months of the disease, the protective parietal pleura is then separated from the visceral pleura. When the caseation reaches the visceral pleura and undergoes liquefaction, a bronchopleural fistula develops, the size of which depends upon the extent of the caseous process involving the pleura. In some cases the rupture may be the result of a subpleural caseous focus located in another part of the lobe, or sometimes in the lower lobe.

There is a very important consideration in evaluating the great frequency of empyema in cases where the pneumothorax is instituted soon after the onset of the disease. The question arises as to whether the greater number of cases of empyema at this stage of the disease is due to the fact that the artificial pneumothorax is instituted in the early months of the disease in a greater number of cases than in the later period. Bendove, Miller, and Alexander (17), in an evaluation of 502 cases from the same institution from which the present series is reported, tabulated the duration of the disease before collapse therapy was attempted. They found that the period between the onset of disease and the attempt at pneumothorax was: one to six months in 195 cases; seven to twelve months in 133 cases; and more than a year in 174 cases. Tubercle bacilli disappeared from the sputum in 52.3 per cent of the first group, 39.8 per cent of the second group, and 33.8 per cent of the third group. These writers also noted that the attempt at pneumothorax was unsuccessful in only 12.8 per cent of the first group, in contrast to 25.4 per cent of the third group.

In many cases in the present series the empyema developed some time after the pneumothorax was started. When a bronchopleural fistula was found at the time of autopsy it was present more often at the basal aspect of the unsuccessfully collapsed cavity in the upper lobe. As the tuberculous cavity progresses it extends toward the visceral pleura. When the caseous process which reaches the pleura undergoes liquefaction, it will result in a communication with the pleural cavity at the point where there is no protective wall to cover it. The fistula usually is situated just below the site where both pleurae became joined. Less often perforations were found in the lower lobes, either in the form of a liquefied caseous focus or a cavity rupturing into the pleural space (figure 5).

In the writer's opinion, the great variation in incidence of empyema as a complication of artificial pneumothorax may in part be explained in the choice of cases and the length of time that an unsuccessful pneumothorax is maintained. The more acute the case the greater the opportunity for spontaneous pneumothorax and an empyema to develop. The longer an artificial pneumothorax is maintained in the presence of a persistent patent cavity, the greater is the opportunity for the vomica to rupture into the pleural space with subsequent infection of the latter.

Tearing of an adhesion: Some authors (4, 18–20) believe that in some instances there is a rupture of existing adhesions with infection of the pleura. Joannides (21) believes that the injured pleura comes in contact with contaminated air and this produces an exudate.

The writer has never seen evidence at autopsy of the rupture of an adhesion band with the subsequent development of an empyema. The development of a bronchopleural fistula following the severance of an adhesion has been observed. The latter phenomenon is a very infrequent occurrence, however, and it is believed that the reason for this lies in the structure of the adhesion bands. Three distinct types of bands are present. One is a thin, cord-like band composed entirely of hyalinized connective tissue, another is a broader round band containing pulmonary tissue for varying extent toward the parietal attachment, and the third consists of wide, fan-like adhesions which always contain lung tissue in its parietal attachment. The fan-like adhesions are dangerous to sever and are usually left intact by the surgeon. The great majority of bands are the thin, hyaline connective tissue bands devoid of lung tissue. Section of these bands at their parietal attachment leads to necrosis of the band which halts at its visceral junction. Support for this thesis is found at autopsy since in a great number of cases all traces of the bands severed by previous Jacobeus operation are absent. Lysis of the round adhesion bands containing lung tissue is a probable cause of fistula formation. Under these circumstances, either the coagulative necrosis extends to the pulmonary tissue or the lung tissue is cut directly, leading to a bronchopleural fistula. Since these adhesions are usually found over cavities, the necrosis extends to the lung tissue until the cavity becomes involved. This may come to open directly into the pleural space (figure 3).

Infection from without: In a previous study (22), it was stated that pyogenic organisms can be introduced into a tuberculous empyema from outside the chest wall by means of aspirations, but that this happens so infrequently that its significance is negligible. Leaver and Hardaway (1) state that, although the introduction of pyogenic organisms during pneumothorax refills and during thoracentesis for removal of serofibrinous exudate is given as an etiologic cause, they could find no case in which this was demonstrated. Berry (23) attributed the development of empyema to faulty technique in 3 of 44 empyema cases in which artificial pneumothorax had been administered.

The evolution of a clear serous effusion into a tuberculous empyema has been noted by a number of different observers, among the first of whom were Brauer and Spengler (24) and Dumarest (25). Peters and Woolley (26) state that it is noteworthy that this evolution may take place unnoticed and that it should be clearly differentiated from septic empyema, especially that due to acute lung perforation. The writer believes that in almost all instances the evolution of a serous effusion into an empyema is the result of a bronchopleural fistula which was not discovered clinically. These are the "silent" fistulas to which reference has already been made. This view is shared by Pollock and Skinner (12) who believe that in the infrequent cases in which this occurs there is a spontaneous

pneumothorax superimposed upon an artficial pneumothorax. The pleuropulmonary fistula, though of only a temporary nature, exists sufficiently long to infect the pleural space with tubercle bacilli.

Empyema necessitatis: Matson (27) believes that empyema necessitatis occurs as the result of the confluence of many infected puncture sites in the pleura and that, as a result of the destruction of larger or smaller areas of the pleura, the purulent exudate invades the subcutaneous tissue and appears as a bulging mass beneath the skin. Sindel (7) does not believe that the aspiration *per se* plays a role in the empyema necessitatis but that the opening in the inelastic, thick, parietal pleura fails to close rapidly.

Rupture into the lung parenchma: There are some references in the literature to the possibility of rupture of the empyema into the lung parenchyma (27, 28, 29). Jehn (28) states that when a cavity lies in the subpleural region, the pleura is relatively thin, so that it is easy for pleural pus to perforate the cavity wall, with a resulting communication between the pleura, cavity, and bronchi. Matson (27) believes that, when a pleural exudate forms rapidly or exists in the pleural cavity for a long time, the lymph passages undergo an obliterative change, preventing resorption of the exudate. He believes that such exudates usually exist under high pressure and, unless evacuated, tend to rupture into the lung.

The writer's experience is against the generally accepted view that an empyema may extend into the lung parenchyma. In each instance where a pulmonary-pleural communication existed, the cause of the opening could always be traced to the lung either in the form of a cavity or a liquefied caseous focus perforating the pleural membrane.

Healing of the empyema may occur, although it is not a frequent occurrence and can only take place in those cases in which the bronchopleural fistula has healed. The underlying pulmonary tuberculosis in these cases also undergoes anatomic healing. In such instances, the fluid within the pleural space is gradually absorbed. The pleural cavity becomes smaller in size but its lumen does not become obliterated. Both the visceral and parietal pleurae become firmer and progressively more cartilaginous in consistency. The inner surface of the pleural cavity loses its rough granular appearance and becomes smooth.

As emphasized by Hedblom (30), the prospect of re-expansion of the lung is poor after a chronic suppurative pleuritis of the productive type, in which the marked thickening of the pleura is added to the fibrotic changes in the lung.

SUMMARY AND CONCLUSIONS

1. In 1,874 consecutive autopsies of chronic pulmonary tuberculosis there were 311 cases of empyema, an incidence of 16 per cent. Two hundred and fifty (81 per cent) were found in the presence of an artificial pneumothorax and 59 (19 per cent) occurred in cases without antecedent treatment. This substantiates the general opinion that empyema is chiefly a complication of artificial pneumothorax.

2. It is our impression that the cause of the empyema in each instance was a bronchopleural fistula.

3. There was no evidence at autopsy of the rupture of an adhesion band in

artificial pneumothorax (due to stretching) with the subsequent development of an empyema.

4. There is no case in the series in which it could be proved that an infection of the pleural space occurred from without.

5. The evolution of a clear serous effusion into an empyema in almost all instances is the result of a bronchopleural fistula which was not discovered clinically.

6. In 180 cases (72 per cent) the artificial pneumothorax was begun within the first seven months of the onset of the disease. Empyema is generally an early complication of the therapy but may appear at any time as long as the collapse is maintained in the presence of an open cavity.

7. In none of the cases in this series was there evidence of the rupture of an empyema into the lung parenchyma.

8. Empyema necessitatis was a complication in thirty-two (9.7 per cent) of the cases. In all but 4 instances they developed in cases of artificial pneumothorax.

SUMARIO Y CONCLUSIONES

El Empiema como Complicación de la Tuberculosis Pulmonar Crónica

1. Entre 1,874 autopsias consecutivas de tuberculosos pulmonares crónicos hubo 311 casos de empiema, o sea una incidencia de 16 por ciento. En 250 (81 por ciento) había presente un neumotórax terapéutico, y 59 (aproximadamente 19 por ciento) correspondían a casos sin previo tratamiento, lo cual apoya la opinión general de que el empiema es principalmente una complicación del neumotórax artificial.

2. Los AA. tienen la impresión de que la causa del empiema consistía, en cada caso, en una fístula broncopleural.

3. No se observaron signos en la autopsia de la rotura (debida a estiramiento) de alguna adherencia en el neumotórax terapéutico, con la subsiguiente producción de empiema.

4. No hay ningún caso en la serie en que pudiera demostrarse que sobrevino del exterior alguna infección del espacio pleural.

5. La evolución de un derrame seroso límpido en empiema en casi todos los casos representa el resultado de una fístula broncopleural que no se descubrió clínicamente.

6. En 180 casos (72 por ciento) se inició el neumotórax terapéutico en término de los primeros siete meses de la iniciación de la enfermedad. El empiema es generalmente una complicación temprana de la terapéutica, pero puede aparecer en cualquier momento en tanto que se mantenga el colapso en presencia de una caverna abierta.

7. En ninguno de los casos de esta serie había signos de la rotura de un empiema en el parénquima pulmonar.

8. El empiema *necessitatis* representó una complicación en treinta y dos (9.7 por ciento) de los casos. En todos, menos 4, se presentó en casos de neumotórax artificial.

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TUBERCULOUS SPONTANEOUS PNEUMOTHORAX[1, 2]

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INTRODUCTION

Despite the fairly frequent occurrence of spontaneous pneumothorax in pulmonary tuberculosis, relatively little has been written concerning this syndrome. Ornstein and Ulmar (1) in their excellent article quote Biach's finding that of 918 cases of spontaneous pneumothorax, 715 were caused by pulmonary tuberculosis. The present study comprises 40 consecutive patients with pulmonary tuberculosis who developed a spontaneous pneumothorax. On the services from which this report is made the complication of spontaneous pneumothorax occurs in about 1.4 per cent of cases of pulmonary tuberculosis, as 14 cases were detected in 1,000 patients with pulmonary tuberculosis who were admitted consecutively. These 40 patients of the present report were studied as a comparison group with a previously reported series of 63 patients with benign idiopathic spontaneous pneumothorax (nontuberculous) (2).

RESULTS OF ANALYSIS OF SERIES

Symptoms: Symptoms of spontaneous pneumothorax vary from none to a sharp, acute, tearing chest pain with dyspnea, cyanosis, and shock. Of the present group of 40 patients, 30 had sudden pain on the affected side. Since most of these patients were moderately ill with pulmonary tuberculosis, it is possible that their pain thresholds were elevated. Effort was not the cause of the tuberculous spontaneous pneumothorax in any patient. Thirty-one patients had moderate to severe dyspnea, although this was not related necessarily to the degree of collapse of the lung. Thirty-two of the 40 patients had chronic cough at the time of their spontaneous pneumothorax.

Physical signs: Physical examination revealed classical signs of pneumothorax, namely, hyper-resonance, absence of breath sounds, and diminished movement of the affected side of the chest. If pleural fluid was present, flatness was noted at the lung base posteriorly. Examination of the chest roentgenograms revealed that 37 of the 40 patients (92 per cent) had pleural adhesions.

Fluid in pleural cavity: Eleven patients had no free pleural fluid. Six patients had only a small amount of fluid up to the level of the diaphragm, and the remaining 23 patients (57 per cent) had fluid above the level of the diaphragm (table 1). This was in marked contrast to the group of benign idiopathic spontaneous pneumothorax patients, in which group there were only 4 cases out

[1] From the College of Medical Evangelists, Los Angeles, The White Memorial Hospital, Los Angeles, and the Pulmonary Diseases Service, Birmingham Veterans Administration Hospital, Van Nuys, California.

[2] Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

of 85 (5 per cent) with fluid above the level of the diaphragm, and in each of the 4 the fluid was grossly bloody.

Extent of pulmonary tuberculosis: Concerning the degree of tuberculosis, 4 had minimal lesions and 36 had either moderately advanced or far advanced pulmonary tuberculosis. Tuberculous spontaneous pneumothorax may affect either side with equal frequency. In this series, 17 patients had a left pneumothorax, 21 had a right pneumothorax, and two had a right spontaneous pneumothorax first, and later a left pneumothorax. Four patients had subcutaneous emphysema.

Course: The patients who developed tuberculous spontaneous pneumothorax usually were at least moderately ill with their pulmonary disease. The sudden onset of a spontaneous pneumothorax, with or without fluid, added to the patient's respiratory embarrassment and toxemia. Fever and tachycardia were common. Secondary infection of the pleural fluid occurred occasionally, presumably through a bronchopleural fistula produced by the tear of the visceral pleura. The pleural fluid was serous at first, but soon became more cloudy and thicker and of higher specific gravity. Examination of the pleural fluid often revealed acid-fast bacilli (10 of 16 cultures, or 63 per cent). Despite the purulent character of the fluid, however, other pyogens were seldom found (two of 14 patients whose fluid was cultured).

The ages of the 40 patients studied varied from 19 to 70 years. Eleven (28 per cent) of the 40 patients died while in the hospital. Death was caused by both the patient's pulmonary disease and his tuberculous spontaneous pneumothorax. The ultimate mortality rate was probably higher. This cannot be definitely stated since most of these patients were transferred to other tuberculous sanatoriums for further prolonged care.

DISCUSSION

Pathogensis: Spontaneous pneumothorax in pulmonary tuberculosis is usually secondary to subpleural caseation with erosion and rupture of the visceral pleura. The site of rupture may be anywhere along the visceral pleura, probably most often in the upper one-third, particularly the anterior and lateral aspect. Air enters the pleural space and the lung on that side collapses.

According to the literature, subcutaneous emphysema is apparently an uncommon finding. Bloomberg and LaTowsky (3) reported a case of a 41 year old male with pulmonary tuberculosis who had a spontaneous pneumothorax, with subcutaneous emphysema and cerebral air embolism. Hurrell (4) reported a 26 year old male with extensive bilateral pulmonary tuberculosis who developed a left spontaneous hemopneumothorax with subcutaneous emphysema of the tissues of the upper half of the chest.

As 4 patients in the present series had subcutaneous emphysema, this complication is apparently more common than is supposed. A possible mechanism is a sudden tear of the parietal pleura as the result of the rush of air into the pleural space and sudden stretching of an adhesion anchored to the parietal pleura. If of sufficient force to tear the parietal pleura, the free air in the

pleural space dissects through the parietal pleural tear into the thoracic wall and subcutaneous tissue.

Diagnosis: The diagnosis of spontaneous pneumothorax is simple if borne in mind. Sudden chest pain, often with dyspnea, plus the physical findings of pneumothorax as previously noted, indicate the correct diagnosis. The chest roentgenogram is helpful in verifying the degree of collapse, presence of pleural adhesions, and the presence and amount of pleural fluid. If the tear of the visceral pleura is slight, the amount of free air in the pleural space may be small and the patient may have no symptoms. In such instances the diagnosis of

TABLE 1

Contrast of Tuberculous Spontaneous Pneumothorax and Benign Idiopathic Spontaneous Pneumothorax

	TUBERCULOUS SPONTANEOUS PNEUMOTHORAX (40 CASES)	BENIGN IDIOPATHIC SPONTANEOUS PNEUMOTHORAX (85 CASES)*
Pulmonary infiltration on chest roentgenogram	100 per cent	0 per cent
Pleural adhesions	92 per cent	0 per cent
Pleural fluid above level of diaphragm	57 per cent	5 per cent (4 patients had grossly bloody fluid).
Immediate hospital mortality rate	28 per cent	0 per cent
Clinically ill	Almost always.	Not usually, and only very briefly (1 to 2 days).
Fever present	Commonly, usually prolonged, and level may be higher (above 100°).	If present, for only a few days, never more than seven days, and low grade (99° to 100°).
After-care required	Continued bed rest and treatment of pulmonary tuberculosis.	None. Patient can return to full activity after collapsed lung has re-expanded.

* Am. J. M. Sc., April 1948, *215*, 427.

spontaneous pneumothorax can be made only by means of a routine chest roentgenogram.

Contrast with benign spontaneous pneumothorax: This study revealed findings in sharp contrast to a previous review of 85 cases of benign idiopathic spontaneous pneumothorax. In the latter group, pleural adhesions were not demonstrable on the chest film, only 5 per cent had fluid above the diaphragm (grossly bloody in each case), uncomplicated expansion was the rule, the mortality rate was zero, and the chest roentgenogram revealed no evidence of pulmonary infiltration. In general, the patient with benign spontaneous pneumothorax was not ill after the initial chest pain and dyspnea. Fever, if present at all, lasted only one or two days. After re-expansion, the patient with benign spontaneous pneumothorax could return to full activity and was completely well.

Treatment: Treatment of spontaneous pneumothorax in the presence of pulmonary tuberculosis depends on the appreciation of the pathological mech-

anisms and resultant symptoms and signs in the individual patient. If the patient is asymptomatic, with no evidence of tension pneumothorax, such as increasing lung collapse, dyspnea, shift of the mediastinum, and no appreciable accumulation of fluid, then he requires no specific therapy. If the visceral pleural tear has been large, or there is a check-valve mechanism, the affected lung will be greatly collapsed and the patient will be dyspneic and cyanotic. In such a situation, enough air should be aspirated from the pleural space to keep the patient comfortable, and this may be repeated as often as necessary. Oxygen should be used freely by tent or BLB mask. If aspirations of air are required very frequently, an indwelling needle inserted through a sterile cork into the pleural space above the level of any pleural fluid, and attached to a water trap, is satisfactory for reducing the increased intrapleural pressure. This indwelling needle should be discontinued as soon as possible (as soon as there is no bubbling of air into the water trap) because of the possibility of infection of the pleural space via the indwelling needle. In most cases, the indwelling needle, when indicated, need remain in the chest wall for twenty-four hours or less.

The management of the complication of pleural fluid varies. Patients with minimal fluid require no thoracentesis. If dyspnea and cyanosis are present, and these are caused primarily by the presence of the pleural fluid, it should be aspirated. Cough is best controlled by codeine by mouth, and by relieving anoxia and tension pneumothorax when they are present. Persistent tuberculous empyema and a bronchopleural fistula which remains patent usually require thoracotomy and later thoracoplasty. As the tuberculosis is active in virtually all of the patients with pulmonary tuberculosis and spontaneous pneumothorax, the use of streptomycin intramuscularly would be indicated. The chemotherapy should be used both for the treatment of the underlying pulmonary disease and for any tuberculous pleuritis present. Mixed infection empyema usually requires thoracotomy with the preoperative and postoperative administration of both streptomycin and penicillin.

In brief, no fixed hard rules of treatment can be drawn up. Each patient is an individual problem. If the pleural space is infected, the responsible organisms should be determined and treatment varied accordingly. If a bronchopleural fistula is present and remains patent, as determined by air samples from the pleural space with oxygen and carbon dioxide determinations, or by the use of methylene blue or oil of peppermint instilled into the pleural space, treatment will vary depending on whether the pleural space is infected and whether a tuberculous or mixed empyema is present. The patient may be so sick and may have such far advanced pulmonary tuberculosis that death occurs rapidly, often within several days.

SUMMARY AND CONCLUSIONS

1. The case records of patients with pulmonary tuberculosis who developed a spontaneous pneumothorax have been reviewed.

2. It was found that the patients were almost always clinically ill with active pulmonary tuberculosis at the time of the pneumothorax.

3. The onset of spontaneous pneumothorax did not seem to be related to effort.

4. Thirty-seven of the 40 patients had pleural adhesions demonstrable on the chest roentgenogram.

5. Twenty-three patients had pleural fluid above the level of the diaphragm.

6. Four patients had subcutaneous emphysema, a finding previously noted only rarely.

7. The immediate hospital case mortality rate was 28 per cent. The total case mortality rate is probably higher as two-thirds of the patients were transferred to other sanatoriums for further care and hence prolonged follow-up observation was not possible.

8. The proper choice of treatment of tuberculous spontaneous pneumothorax depends upon a number of variables, such as the presence or absence of pleural fluid or tension pneumothorax.

SUMARIO Y CONCLUSIONES

Neumotórax Espontáneo Tuberculoso

1. Este estudio abarcó las historias clínicas de tuberculosos pulmonares que manifestaron neumotórax espontáneo.

2. Observóse que los sujetos se hallaban casi siempre clínicamente enfermos con tuberculosis pulmonar activa al presentarse el neumotórax.

3. La iniciación del neumotórax espontáneo no guardaba al parecer relación con el esfuerzo.

4. Treinta y siete de los 40 enfermos tenían adherencias pleurales observables en las radiografías torácicas.

5. Veintitrés enfermos tenían derrames pleurales más arriba del nivel del diafragma.

6. Cuatro enfermos tenían enfisema subcutáneo, hallazgo este raramente observado antes de ahora.

7. La morboletalidad hospitalaria inmediata representó 28 por ciento, pero la total es probablemente mayor, dado que dos terceras partes de los enfermos fueron trasladados a otros sanatorios para asistencia ulterior, lo cual impidió prolongar la observación subsiguiente.

8. La elección del tratamiento más apropiado para el neumotórax espontáneo tuberculoso depende de varios factores, tales como la presencia o ausencia de derrame pleural o de neumotórax de tensión.

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THE USE OF AUREOMYCIN IN PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

The need for an effective therapeutic agent in the treatment of pulmonary tuberculosis has long been recognized. Although streptomycin has proved to be of value, it is not completely satisfactory because of the frequent development of resistant strains of tubercle bacilli. Furthermore, the high incidence of vestibular dysfunction, which occurs in streptomycin-treated patients, is an additional drawback to its use. For these reasons the search has continued for a drug which would have tuberculostatic properties without the toxic properties of streptomycin.

Aureomycin, an antibiotic derived from a mold, *Streptomyces aureofaciens*, appeared to be a drug worthy of trial in the treatment of pulmonary tuberculosis. It is supplied as the yellow crystalline hydrochloride, highly soluble in water, in which it gives an acid solution with a pH of 4.5. Aureomycin is fairly stable in acid solution but deteriorates rapidly at room temperature in alkaline solution. It is much more effective in acid media than in alkaline, the reverse of streptomycin (1). The emergence of resistant organisms has not been encountered during its *in vitro* or *in vivo* use and there is no evidence of cross-resistance with penicillin, polymyxin, or bacitracin. Aureomycin is rapidly absorbed from the gastrointestinal tract, promptly excreted in the urine, and can be given by mouth (2, 3). The drug has already been shown to have a wide spectrum of activity against many bacteria (4, 5, 6, 15, 16), rickettsia (7, 8, 9, 10, 11), and viruses (4, 8, 12, 13, 14). Duggar (17), using a plate-zone technique, found inhibition of the growth of tubercle bacilli in the presence of growing strains of *Streptomyces aureofaciens*.

Because of these properties and the need for chemotherapeutic agents other than streptomycin in pulmonary tuberculosis, 3 patients with active, exudative forms of this disease were intensively treated with aureomycin.

OBSERVATIONS

Three patients with pulmonary tuberculosis, 2 with tuberculous pneumonia and one with a recent definitely dated exudative "spread", which occurred while the patient was on bed rest in the hospital, were treated with aureomycin[2]. Frequent roentgenograms, sputum smears and cultures for tubercle bacilli, erythrocyte sedimentation rates, complete blood counts, and urinalyses were

[1] From the Division of Pulmonary Diseases, Montefiore Hospital, Bronx, N. Y., and The Montefiore Country Sanatorium, Bedford Hills, New York.

[2] Aureomycin hydrochloride ("Duomycin") was supplied by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

obtained on all the patients. In addition, liver function tests were obtained in one patient at weekly intervals.

Case Reports

Case 1: (E. D.), a 31 year old white female, with a history of a tuberculous infiltrate in the left upper lobe since 1945, was admitted to the Montefiore Country Sanatorium on March 2, 1948. Three months prior to entry she gave birth to a normal living child. Review of her serial roentgenograms revealed slight regressive changes during 1946 and 1947, and her sputum had been negative for tubercle bacilli for nine months. Nevertheless, it was ap-

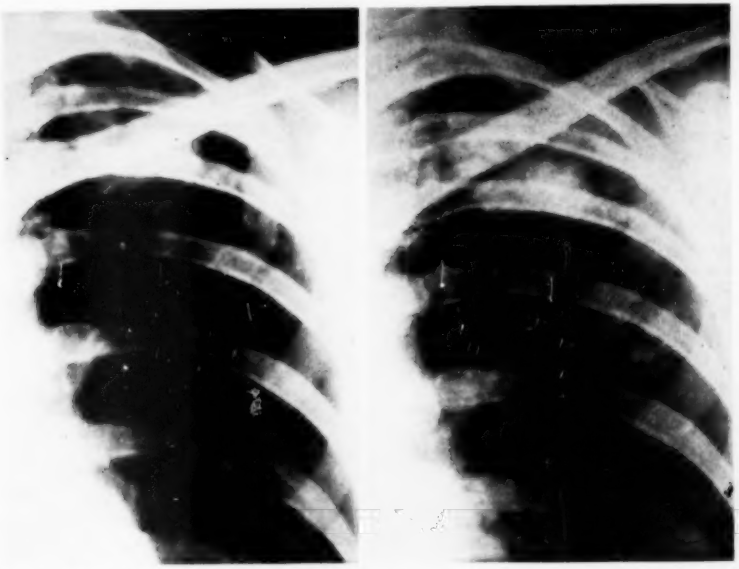


FIG. 1. (E. D.) (Left) September 15, 1948. Recent exudative lesion of the left upper lobe before institution of aureomycin therapy.

FIG. 2. (E. D.) (Right) December 6, 1948. Increase in infiltration in left upper lobe after ten weeks of aureomycin therapy.

parent from her admission roentgenogram that she would probably require active therapy as the lesion appeared "soft" and contained radiolucencies suggesting breakdown. The patient was observed on bed rest for four months without any apparent change on repeated roentgenographic examinations. Her temperature was normal and sputum smears and cultures were negative for tubercle bacilli. In August, 1948 there was an increase in cough and sputum and a wheeze was heard over the left upper lobe. The sputum revealed tubercle bacilli on smears, and roentgenographic examination (figure 1) showed extensive exudative progression of the lesion in the left upper lobe. Bronchoscopic examination revealed acute inflammation at the orifice of the left upper lobe bronchus but no ulceration or granulation. Aureomycin in sixth molar sodium lactate was started intravenously on September 16, 1948. The dose was gradually increased from 300 to 600 mg. twice daily for eight days, at which time the intravenous route of administration was discontinued because of a low grade phlebitis at the sites of injection. Nausea and some drowsiness occurred during intra-

venous administration of the drug. Therapy was instituted by the oral route on the twelfth day of treatment in a dosage of 500 mg. every three hours, a total of 4.0 Gm. a day. This was continued until December 18, 1948 (except for ten days when no drug was avail-

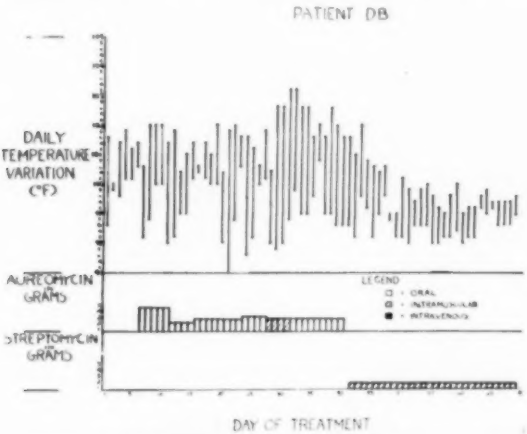


FIG. 3. (D. B.) (Top) Illustrates the clinical course of a patient treated with aureomycin followed by streptomycin.

FIG. 4. (D. B.) (Lower left) October 11, 1948. Tuberculous pneumonia of right upper lobe with bronchogenic spread to right lower lobe. Appearance before institution of aureomycin therapy.

FIG. 5. (D. B.) (Lower right) November 20, 1948. The appearance of the lesion after five weeks of aureomycin therapy.

able) for a total of ninety-four days of treatment. The drowsiness present during intravenous therapy was not noted when the drug was given by mouth. Nausea, vomiting, and anorexia occurred occasionally during oral therapy. Clinical and laboratory observations revealed no alteration in renal or hepatic function nor in the cellular constituents of the

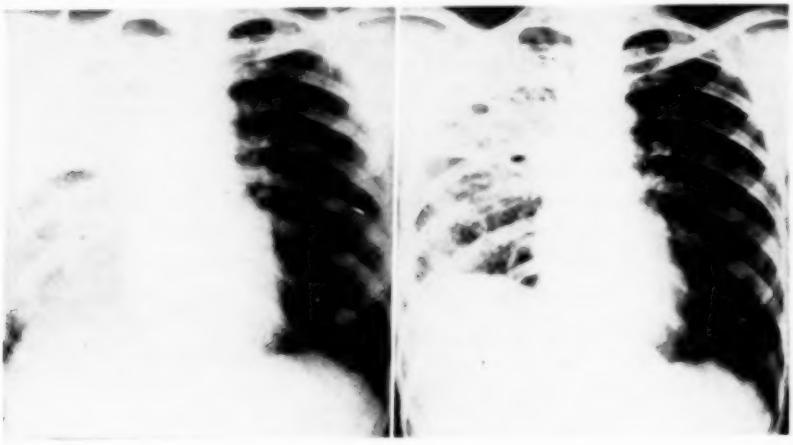
peripheral blood. The temperature was normal throughout the period of therapy. There was some reduction in cough and a decrease in sputum from 15 Gm. to 2 Gm. daily. Nevertheless, the sputum remained positive for tubercle bacilli on direct smear. Serial roentgenograms of the lungs revealed only slight hardening of the peripheral portions of the lesion during the first seventy-five days of treatment. During the third month of therapy a wheeze reappeared over the left upper lobe and the roentgenogram of December 16, 1948 (figure 2) showed an increase in the exudative infiltration in the left upper lobe. Bronchoscopy performed on December 16, 1948 revealed for the first time the presence of granulation tissue at the orifice of the left upper lobe bronchus.

The patient had received a total of 300 Gm. of aureomycin over a period of ninety-four days. Because of the failure to respond to aureomycin and the progression of the disease, the patient was started on a short course of streptomycin preliminary to the induction of a left artificial pneumothorax.

Case 2: (D. B.), a 26 year old Negro female, was admitted to Montefiore Hospital on October 8, 1948 with a history of cough, fever, weakness and weight loss of two months' duration, and a single hemoptysis two weeks prior to admission. This patient's course is illustrated in figure 3. On entry the patient had a temperature of 102° F. Dullness, bronchovesicular breath sounds, and rales were heard on examination over the right upper lobe and at the right base. The sputum was positive for tubercle bacilli on direct smear. The erythrocyte sedimentation rate was 90 mm. in one hour (Westergren method) and the blood leukocyte count was 15,750 with a shift to the left. A chest roentgenogram obtained October 11, 1948 (figure 4) showed an extensive pneumonic lesion of the right upper lobe with bronchogenic spread to the right lower lobe. The patient received aureomycin by mouth every four hours from the seventh to the fortieth day of treatment, in doses ranging from 1.5 to 4.0 Gm. a day. A total of 72 Gm. of aureomycin was employed over a period of thirty-four days. Some nausea, vomiting, and diarrhea were noted when the larger doses were administered and the patient lost several pounds in weight. Slight resorptive changes were noted on the chest roentgenogram (figure 5) but the spiking temperature continued and the sputum remained positive for tubercle bacilli on direct smear. Streptomycin 1.0 Gm. a day was substituted for the aureomycin on the forty-second day of treatment. The effect was promptly apparent in the temperature curve as indicated in figure 3. The temperature returned to normal within several days. Serial roentgenograms showed some clearing of the lesion within fourteen days after streptomycin was started. The patient soon developed a sense of well-being and gained weight. Right artificial pneumothorax was induced on the sixty-third day of treatment.

Case 3: (B. H.), a 30 year old Negro female, was admitted to the Montefiore Hospital on September 13, 1948 with a history of weakness, fever, and weight loss of four weeks' duration. At the time of admission the patient's temperature was elevated to 105°F. and she appeared acutely ill. Signs of consolidation over the entire right lung were elicited on physical examination. The sputum was positive for tubercle bacilli on direct smear; the erythrocyte sedimentation rate was 83 mm. in one hour (Westergren method); there was a moderate microcytic normochromic anemia; and the blood leukocyte count was elevated to 13,450 with a shift to the left. A roentgenogram of the chest (figure 6) showed consolidation of the right upper lobe with an extensive exudative infiltration of the right middle and right lower lobes. Intravenous aureomycin in sixth molar sodium lactate, in gradually increasing doses from 300 to 1,000 mg., was administered from the first to the sixteenth day of treatment. This was discontinued because of a low grade phlebitis at the sites of injection and oral administration of the drug was substituted. During intravenous therapy, drowsiness and some confusion were noted for a brief period. The drowsiness disappeared when intravenous therapy was stopped. The patient then received 4.0 Gm. of aureomycin orally per day in 6 doses from the seventeenth to the forty-third days and 2.0 Gm. a day from the

fifty-fourth to the sixty-fifth days of therapy. For four days during the last period the drug was administered intramuscularly in a dose of 2.0 Gm. per day. The total dosage of aureo-



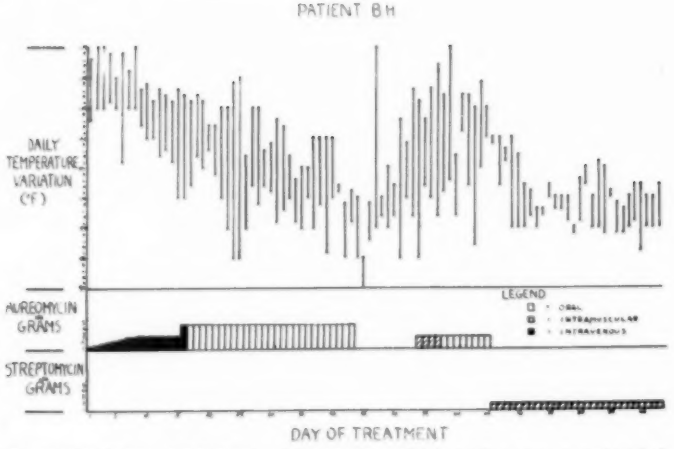


FIG. 6. (B. H.) (Upper left) September 13, 1948. Tuberculous pneumonia of the right upper lobe with extensive exudative involvement of right middle and right lower lobes prior to aureomycin therapy.

FIG. 7. (B. H.) (Upper right) November 20, 1948. Following eight weeks of aureomycin therapy extensive cavitation throughout the right lung is noted. The right leaf of the diaphragm is elevated.

FIG. 8. (B. H.) (Bottom) Illustrates the clinical course of a patient treated with aureomycin followed by streptomycin. Note febrile state responds to streptomycin but not to aureomycin.

mycin was 168 Gm. over a period of sixty-five days. During oral therapy occasional vomiting, diarrhea, a weight loss of 10 pounds, and transitory albuminuria were noted. Cough

and the amount of sputum decreased; the erythrocyte sedimentation rate dropped from 88 mm. to 33 mm. in one hour; and the temperature decreased temporarily but again rose to 105°F. by the time the drug was discontinued. While the patient was receiving aureomycin, progressive excavation occurred in the right lung (figure 7) and the sputum remained positive for tubercle bacilli. During this period spontaneous right diaphragmatic paralysis appeared, probably due to involvement of the phrenic nerve in the thorax by tuberculous mediastinal nodes. Streptomycin 1.0 Gm. per day was substituted for aureomycin on the sixty-sixth day of treatment with prompt decrease in fever and improvement in the patient's general condition (figure 8).

Additional Studies

The tubercle bacilli recovered from the sputum of patient E. D. prior to treatment were tested for *in vitro* sensitivity to aureomycin. Primary isolation of the bacilli on Petragnani's medium was followed by subculture on Dubos' liquid Tween-albumin medium (18). From a diffusely, actively growing 11 day old culture, 0.1 cc. inocula were put into a series of tubes of Dubos' Tween-albumin medium which contained various concentrations of aureomycin. The tubes were incubated for nineteen days. Growth of the organisms was found to be inhibited by concentrations of 10 and 100 γ of aureomycin per cc. No inhibition after the first five days was observed in tubes containing one γ of aureomycin per cc.

Bio-assays[3] of the serum of this same patient for aureomycin revealed the presence of the drug in concentrations up to 8.0 γ per cc. two hours after an intravenous dose of 400 mg. and 1.6 γ three hours after an oral dose of 500 mg. These were the highest concentrations obtained. In patient B. H. (case 3) a concentration of 4.0 γ per cc. of serum was obtained four hours after an oral dose of 700 mg. of aureomycin.

COMMENT

The difficulties in the evaluation of the effectiveness of new therapeutic agents in patients with pulmonary tuberculosis are well known. In order to preclude some of these difficulties in this study, patients were selected with pneumonic involvement, elevated temperature, and evidences of acute illness of apparently recent onset, or with definitely dated recent spread. One patient (D. B.) showed minimal regression radiographically and another (B. H.) showed progressive excavation during aureomycin therapy. In these 2 patients the high fever persisted and the decrease in the severity of the illness was not disproportionate to what might be expected from bed rest alone. The prompt and striking improvement in these patients when streptomycin was used illustrated that the disease could be effectively treated by an antibiotic. In patient E. D. therapy was directed against a new exudative infiltrate and an early bronchial lesion. Progression of both the parenchymal and the bronchial disease was demonstrated during the patient's third month on aureomycin treatment. With streptomycin this is an extremely rare occurrence unless drug-fastness has developed.

The toxic manifestations of aureomycin when given orally for a prolonged

[3] Bio-assays were performed by Mr. A. C. Dornbush of the Lederle Laboratories, using the tube dilution method and a strain of *B. cereus* known as Bacillus No. 5 (3).

period were minimal. Slight nausea, vomiting, and diarrhea were noted. The transitory albuminuria which occurred probably was due to the febrile state of the patient. During intravenous therapy a low grade phlebitis invariably developed and when the drug was given intramuscularly the patients complained of intense pain at the sites of injection.

SUMMARY

Aureomycin was used for periods ranging between thirty-four and ninety-four days in the treatment of 3 young adult patients with acute, extensive, exudative forms of pulmonary tuberculosis. The oral route of administration was more satisfactory than the parenteral route because adequate serum levels were obtained and there was little, if any, toxic effect. Although the drug was found to have tuberculostatic properties *in vitro*, there was no improvement in the patients studied in this investigation. Streptomycin employed as a control therapeutic agent effectively controlled the spread of the tuberculous process.

SUMARIO

Empleo de la Aureomicina en la Tuberculosis Pulmonar

La aureomicina fué empleada en el tratamiento de 3 adultos jóvenes con formas exudativas, extensas y agudas de tuberculosis pulmonar. La droga fué administrada durante períodos de 34 a 94 días. La vía oral de administración resultó más satisfactoria que la parentérica, por obtener adecuados tenores séricos y producir poco, o ningun, efecto tóxico. Aunque la droga mostró propiedades tuberculostáticas *in vitro*, no hubo mejoría en los enfermos estudiados. La estreptomicina, empleada como terapéutica testigo, cohibió eficazmente la difusión del proceso tuberculoso.

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QUESTION OF CONTAGION IN COCCIDIOIDOMYCOSIS. STUDY OF CONTACTS[1,2]

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INTRODUCTION

Recent interest in coccidioidomycosis has resulted from the fact that a large percentage of the hundreds of thousands of military personnel who trained in the Southwest desert area became infected.

It has been shown that the life cycle of the fungus coccidioides immitis consists of two stages: (*1*) a saprophytic stage in the soil found in the desert regions; and (*2*) a parasitic stage in man and animals. It has been believed that the soil (saprophytic) phase could not be by-passed, that man becomes infected by inhalation of the contaminated dust, and that acute infection does not pass from person to person via sputum containing the endospores or spherules (1, 2, 3).

Rosenthal and Routien (4, 5) recently reported, however, that by direct instillation of fungus (spherule) laden material into the respiratory tract of guinea pigs, they were able to infect the lungs of these animals. The material used consisted of undiluted sputum and pus and of emulsions of human granulation tissue and lymph nodes from infected cases. This material was instilled through an opening made in the trachea and was then propelled downward by several injections of air. As a result of these experiments, the authors postulated that spherule-containing material is infectious for guinea pigs when instilled into the lungs. They concluded that active primary or progressive coccidioidomycosis in human beings should be considered contagious until proved otherwise.

The present writers have under observation at this time a group of World War II veterans with residuals of pulmonary coccidioidomycosis. A clinical analysis of these cases has been submitted for publication elsewhere (6). These veterans were all formerly stationed in the Southwest endemic area. All of them returned to their homes in New York City between 1943 and 1946 and have been living with their families from six months to five years. It was felt that, because of the public health aspects involved, it would be important to learn if coccidioidal infection had occurred in the personal family contacts of these cases. To the knowledge of the writers, no study of coccidioidomycosis contacts living outside the endemic area has yet been reported.

METHOD

Contacts of six cases showing a residual pulmonary coccidioidal cavity on chest roentgenograms were investigated. Cases with residual pulmonary nod-

[1] From the Thoracic Unit, New York Regional Office, Veterans Administration.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

ules or other types of lesions were eliminated. It is felt that the cavity cases would be more likely to infect contacts.

Examinations of the sputum for coccidioidal spherules prior to the return of the veterans to their families were reported negative in 3 of the cavity cases. No record of the sputum findings is obtainable in the remaining 3 cavity cases.

Coccidioidal spherules are not readily recovered from sputum in cases of pulmonary coccidioidomycosis. In 225 cases studied by C. E. Smith[3] the fungus

TABLE 1

Results of Study of Contacts of Cases of Cavitary Coccidioidomycosis

CASES	TYPE OF DISEASE	CONTACT	DURATION OF CONTACT	SKIN TEST OF CONTACT COCCIDIOIDIN 1/100	CHEST ROENTGENOGRAM OF CONTACT
			months		
Case 1	Coccidioidal cavity	Wife—Age 25	30	Negative	Negative
		Brother—Age 23	30	Negative	Negative
Case 2	Coccidioidal cavity	Wife—Age 21	24	Negative	Negative
Case 3	Disseminated coccidioidomycosis (skin, lung)	Wife—Age 27	6	Negative	Not done
Case 4	Coccidioidal cavity	Sister—Age 34	32	Negative	Not done
		Brother in-law—Age 39	32	Negative	Not done
		Nephew—Age 3	32	Negative	Not done
Case 5	Coccidioidal cavity	Wife—Age 29	41	Negative	Negative
		Son—Age 3	41	Negative	Negative
		Daughter—Age 4	41	Negative	Negative
Case 6	Coccidioidal cavity	Wife—Age 23	60	Negative	Negative
Case 7	Coccidioidal cavity	Daughter—Age 2½	24	Negative	Negative

was recovered from only 42 per cent of the cases. These cases were studied in the early stages of infection when the fungus can more readily be demonstrated.

In addition to the cavity cases, a contact to a case of disseminated disease was studied. For obvious reasons, only contacts who had never been in the coccidioidomycosis endemic area were selected for study. All contacts received an intradermal skin test using 0.1 cc. of 1:100 dilution of potent coccidioidin obtained from Dr. C. E. Smith of Stanford University and, where possible, a roentgen film of the chest.

[3] Smith, C. E.: Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health, 1940, *30*, 600.

RESULTS

Eleven contacts of 6 cavity cases and one of a case of disseminated disease were examined (table 1). All chest roentgenograms and coccidioidin skin tests of these contacts were negative. If infection had occurred in any of the contacts examined, it would have been expected that a positive coccidioidin skin test would have developed. A positive skin test is known to appear within a week or two after infection and to persist for many years (7).

The results obtained in this study indicate that following a period of six to sixty months of intimate exposure to cases of coccidioidomycosis with pulmonary cavitation none of the contacts had become infected. Although the total number of contacts investigated is not large, it is believed that clinical evidence against the concept of man to man contagion has been shown. Concerning Rosenthal's experiments in the transmission of coccidioidomycosis from man to animals, it should be pointed out that the procedure of direct forceful instillation of infected material into the respiratory tract of guinea pigs goes far beyond the normal relationships obtaining in human beings.

SUMMARY

1. Evidence bearing on the question of contagion in coccidioidomycosis is presented.

2. Eleven contacts of patients with cavitary pulmonary coccidioidomycosis and one contact of a patient with disseminated coccidioidomycosis were studied with chest roentgenograms and coccidioidin skin tests.

3. The roentgenograms and coccidioidin skin tests of all contacts were negative, indicating that none of the contacts had become infected during a period of six to sixty months of exposure.

4. It is believed that additional clinical evidence has been obtained that coccidioidal infection from man to man does not occur.

SUMARIO

El Problema del Contagio en la Coccidioidomicosis: Estudio de los Contactos

1. Preséntanse datos relativos a la cuestión del contagio en la coccidioidomicosis.

2. Once contactos de enfermos con coccidioidomicosis pulmonar cavitaria y un contacto de un enfermo con coccidioidomicosis difusa fueron estudiados con radiografías torácicas y cutirreacciones a la coccidioidina.

3. Las radiografías torácicas y las cutirreacciones a la coccidioidina resultaron negativas en todos los contactos, indicando esto que ninguno de ellos se había infectado durante un período de seis a sesenta meses de exposición.

4. Opinan los AA. que estos datos clínicos aportan neuva prueba de que no ocurre infección coccidioidea de persona a persona.

Addendum

Since this paper was submitted for publication, a reference has been made by Dr. C. E. Smith[4] to several contacts who were studied by him for contagiousness. These contacts were negative to coccidioidin skin testing.

Acknowledgement

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PULMONARY INFILTRATION ASSOCIATED WITH SENSITIVITY TO HISTOPLASMIN[1,2]

Report of a Case

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(Received for publication May 7, 1948)

INTRODUCTION

As a result of extensive investigation by many workers, particularly those associated with the U. S. Public Health Service, it is becoming increasingly clear that many instances of pulmonary calcification are not the result of previous infection by the tubercle bacillus but, rather, represent the end stage of infection by Histoplasma capsulatum. This suggestion was first propounded by Smith (1) and later elaborated and confirmed by Palmer (2, 4) and by Christie and Peterson (3, 5). Histoplasmin-positive and tuberculin-negative cases of pulmonary calcification were observed to be particularly prevalent in the East Central states. An especially high incidence was noted in the Kansas City area.

Pulmonary calcification associated with histoplasmin sensitivity cannot be differentiated roentgenologically from that which results from tuberculous involvement. This has been emphasized recently by Riley (6). It follows then that the precursors of these calcifications might also show similar features and likewise be indistinguishable. That such is indeed the case has been clearly demonstrated by Furcolow, *et al.* (7). Persistent pulmonary infiltration with histoplasmin sensitivity and tuberculin anergy occurred on 72 occasions among school children in Kansas City, Missouri. Approximately two-thirds of these lesions were nodular and sharply circumscribed. One-fourth were diffuse, patchy, soft lesions which occasionally developed into nodular lesions; a few showed only lymph node involvement, and a few were of the disseminated type. Sontag and Allen (8) also described similar precalcific lesions in Ohio children who were sensitive to histoplasmin but not to tuberculin. It is obvious that the characteristics of these lesions are similar in every way to those of tuberculous infiltrations and that the only means of differentiation at the present time, besides the actual isolation of the offending organism, rests with skin tests. Attempts at isolation of the organism in this type of case have met with little success up to the present time. In only one case was Histoplasma capsulatum recovered (9).

The practical importance of pulmonary lesions associated with histoplasmin sensitivity occurring in individuals who do not react to tuberculin cannot be

[1] From the Tuberculosis Section, Medical Service, Veterans Administration Hospital, Fort Logan, Colorado, and the University of Colorado School of Medicine, Denver, Colorado.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

overemphasized. Such lesions, if not carefully investigated and studied, may lead to an erroneous diagnosis of tuberculosis. Such a case is described below.

CASE REPORT

A twenty six year old white male veteran was admitted to the Tuberculosis Section, Veterans Administration Hospital, Fort Logan, Colorado, on July 24, 1947 with a diagnosis of active minimal pulmonary tuberculosis.

In October, 1946 the patient sought employment with a large corporation in Dayton, Ohio. A routine pre-employment chest film revealed bilateral upper lobe disease, minimal in extent. He was told that he had tuberculosis and that he should seek hospitalization. This advice was ignored, and in June, 1947, the patient prepared to enter a university. Routine stereoscopic photofluorograms again revealed pulmonary disease and hospitalization was advised.

On admission to the hospital, no symptoms referable to the respiratory system were elicited. The past history included pertussis, followed by a moderately severe episode of pneumonia at the age of 8. Scarlet fever, without sequelae, occurred at the age of 23. System review was entirely negative.

The patient's geographical history was as follows: He was born in Springfield, Ohio, where he remained until the age of 12. He lived in Cincinnati, Ohio, from the age of 12 to 24. He lived in Dayton, Ohio, for one year and then entered the Navy in 1943. He spent four months at Great Lakes, Illinois, four months in Gulfport, Mississippi, nine months in Chicago, Illinois, two months in New York City, eight months on duty in the Atlantic and Caribbean waters, one month in San Diego, California, and eight months in the Pacific and Hawaiian waters. He was separated from the Service in Chicago, Illinois, in April, 1946. Since that date, he has spent one year in Dayton, Ohio, and five months in Colorado.

Physical examination revealed the following: height, 5′8½″; average weight, 150 pounds; present weight, 150 pounds; and temperature, 98.6°F. The patient was a well developed and well nourished white male who did not appear to be acutely or chronically ill. He was not dyspneic, cyanotic, or jaundiced. Examination of the head and neck revealed no abnormalities. The pupils were equal and regular and reacted to light and accommodation. The sclerae and conjunctivae were normal. External occular movements were normal. Funduscopic examination revealed no abnormalities. Ear, nose, and throat examination was normal. The gag reflex was present and the teeth were in good repair. Examination of the chest showed a normal thoracic cage. Respiratory movements were equal and symmetrical. The lungs were clear; no rales were noted. The heart was not enlarged. The cardiac rhythm was regular and no murmurs were detected. The pulse was 80 per minute and the blood pressure in mm. of mercury was 120 systolic and 78 diastolic. The abdomen was soft and no masses were palpable. The liver, spleen, and kidneys were not clinically enlarged. The genitals were normal. Rectal examination revealed no abnormalities. The prostate was normal in size, shape, and consistency. Neurological examination was grossly normal. No lymphadenopathy was noted.

Laboratory data were as follows: RBC 5.64 million, hemoglobin 15 Gm., WBC 10,300, neutrophils 57, lymphocytes 39, monocytes 3, eosinophils 1. The erythrocyte sedimentation rate was 4 mm. per hour (Wintrobe). A blood Kahn test for syphilis was negative. Urinalysis was normal.

The following skin tests were performed:

July 30, 1947:

Second strength tuberculin, 0.005 mg. Negative reaction (purified protein derivative)

Coccidioidin, 1:100 Doubtful reaction

Histoplasmin, 1:100 2+ reaction

September 1, 1947:

Old Tuberculin, 0.1 mg. Negative reaction

September 5, 1947:

Old Tuberculin, 1.0 mg. Negative reaction

September 17, 1947:

Second strength tuberculin, 0.005 mg. Negative reaction (purified protein derivative)

Coccidioidin, 1:100 Negative reaction

Histoplasmin, 1:100 2+ reaction

December 15, 1947:

Blastomycin, 1:1,000 Negative reaction

Two specimens of sputum and six gastric washings were negative for tubercle bacilli after eight weeks' culture. Examinations of sputum and gastric washings for Histoplasma capsulatum on smear, culture, and animal inoculation were also negative.

Sternal marrow aspiration was performed on September 22, 1947.[3] Bone marrow smears prepared and stained by Wright and Giemsa stains failed to reveal the presence of the fun-

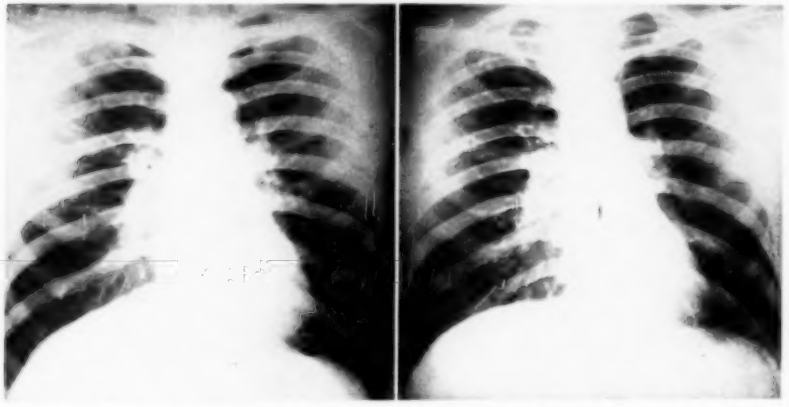

FIG. 1a. (Left) Chest roentgenogram, October, 1946. Soft, exudative infiltration is visible in the right first anterior interspace. The more fibrotic disease in the left first anterior interspace is barely visible.

FIG. 2a. (Right) Admission chest roentgenogram, July, 1947. The lesion in the right first anterior interspace is now nodular and fibrotic in character.

gus. Culture of the aspirated material was also negative for fungi. Two guinea pigs and 4 white mice were inoculated with specimens of bone marrow. The animals were sacrificed a month following inoculation, and blood smears, as well as smears from the liver and spleen, were negative for Histoplasma capsulatum. Microscopic examination of liver, spleen, lung, kidney, and adrenals revealed no histological evidence of infection by the fungus.

The chest roentgenogram on admission to Fort Logan revealed a minimal productive lesion in the first anterior interspace on the right. A small radiolucent area was present within the density. A smaller fibrotic infiltration was also noted at the periphery of the left first anterior interspace. Apical lordotic films failed to reveal the presence of definite excavation. Fortunately, it was possible to obtain the previous films dated October 18, 1946, taken in Dayton, Ohio. They exhibited a rather soft minimal infiltration in the right first anterior interspace, as well as a more fibrotic lesion in the left first anterior interspace (figures 1a and 1b). A comparison between these films and the admission roentgenograms

[3] These studies were performed by Dr. W. J. Tomlinson, Chief of Laboratory Service, Veterans Administration Hospital, Fort Logan, Colorado.

at Fort Logan revealed that a definite degree of absorption had occurred in the right upper lobe lesion in the nine month interval between the two sets of films. Not only had this density become smaller, but it had also assumed a more productive character. The same was true, to a less extent, of the left-sided lesion (figures 2a and 2b). In view of these changes, it was considered that the lesions certainly were active in October, 1946 and had

FIG. 1b. (Upper) Enlargement of lesion in right first anterior interspace revealing its soft character.

FIG. 2b. (Lower) Enlargement of lesion in right first anterior interspace. The nodular character of the disease is well visualized.

regressed at the time of admission. Subsequent serial chest films taken at monthly intervals up to December, 1947 have revealed no change in the extent of the disease but the lesion in the right first anterior interspace appears to have become even harder and more fibrotic in character.

The patient's hospital course was entirely uneventful. He was asymptomatic and afebrile throughout. He was placed on strict bed rest on the assumption that his disease was tuberculous in origin. As soon as subsequent studies revealed that such a diagnosis was untenable, however, this rigid regimen was abandoned.

Because of the doubtful coccidioidin skin reaction, coccidioidal serological studies were performed on October 27, 1947. Both the precipitin and complement fixation tests were entirely negative. In November, 1947 histoplasmin and blastomycin serological studies were also performed. The histoplasmin complement fixation test was negative and the blastomycin complement fixation reaction was so slight as to be called negative.

COMMENT

This case meets the three criteria established by Furcolow, *et al.* (7) for possible subclinical cases of histoplasmosis: (*1*) the individual has skin sensitivity to histoplasmin but not to tuberculin; (*2*) the lesion must persist at least two months; and (*3*) laboratory and clinical examinations exclude the presence of tuberculosis and other conditions such as sarcoidosis or Hodgkin's disease.

The failure to isolate tubercle bacilli on repeated attempts, coupled with the persistent tuberculin anergy in the presence of an active lesion (admittedly regressive), make it difficult to label this patient's pulmonary disease as tuberculosis. Houck (10) in an editorial comment emphasized the recent concept that histoplasmosis, instead of being a rare and fatal disease, may be a common and benign infection occurring in a large part of the population of some areas in the Middle West. He stressed the importance of considering the patient's history of residence in endemic areas and the use of appropriate skin tests in the investigation of pulmonary lesions. The reaction to histoplasmin and the long period of residence in what may be termed an endemic area (Ohio) lend support to the belief that this case may represent such a benign type of histoplasmosis as is postulated by Houck.

As noted above, the histoplasmin complement fixation test on this patient's serum was negative. The exact significance of this procedure as a diagnostic measure remains undetermined. The studies of Furcolow and his associates at Kansas City are expected to shed some light on this question. It may be stated with some degree of confidence, however, that negative serological studies do not necessarily eliminate histoplasma as the etiological agent. Some support for this statement may be obtained from the experience with serological studies in coccidioidal infections. In quiescent coccidioidal lesions (with normal erythrocyte sedimentation rates), the complement fixation tests are usually negative (1). If these findings may be transferred to the field of histoplasmotic infections, serological studies in the regressive lesions, as illustrated by this case, would also be expected to yield negative results.

The question of the further management of such a case merits some discussion. There can be little argument with the view that during the period of investigation the case should be treated as one of tuberculosis. The value of strict bed rest in minimal tuberculosis has been adequately demonstrated by Amberson (11), and such a regimen should be immediately instituted. However, when the diagnosis of tuberculosis is shown to be in error by the negative results of skin tests and the failure to obtain tubercle bacilli in sputum and gastric washings by culture and/or guinea pig inoculation, it would appear that such a rigid therapeutic schedule is no longer required. Admittedly, the entire picture of the entity "benign histo-

plasmosis" has not yet been fully observed and, accordingly, definitive statements regarding therapy cannot be made. The supposition that these cases require little or no treatment has no basis in fact, however, and conceivably could lead to serious harm. The tendency following the exclusion of tuberculosis as a diagnosis is to allow the patient unrestricted activity. This conclusion is naturally drawn from the investigations emphasizing the close correlation between histoplasmin sensitivity and pulmonary calcification (2, 3, 4 and 5). The innocuousness of "benign histoplasmosis" has been emphasized by Houck (10). The excellent observations, however, of Sontag and Allen (8) on 170 normal southwestern Ohio children sounds a note of caution. While none of their histoplasmin-positive children who exhibited pulmonary lesions presented symptoms comparable to those seen in cases of proved histoplasmosis, the serial growth data and illness histories of these children strongly suggest that the growth progress and health pattern may be significantly different from the negative histoplasmin reactors. In the light of these observations, it would appear that at the very least these patients should be closely observed and followed with serial clinical laboratory and roentgenographic studies.

SUMMARY

A case of pulmonary infiltration with tuberculin anergy and histoplasmin sensitivity is reported. The possibility of such a case representing an instance of "benign histoplasmosis" is discussed. The danger of confusing such cases with tuberculosis is emphasized and the broad aspects of management of such a case are reviewed.

SUMARIO

Infiltración Pulmonar Asociada a Sensibilidad a la Histoplasmina

Comunícase un caso de infiltración pulmonar con anergia tuberculínica y sensibilidad a la histoplasmina, discutiéndose la posibilidad de que represente un caso de "histoplasmosis benigna." Recálcase el peligro que entraña la confusión de esos casos con tuberculosis y repásase, a grandes trazos, la asistencia de los mismos.

Acknowledgments

The coccidioidin employed in this case was supplied by Dr. Charles E. Smith of Stanford University, California, who also performed the coccidioidal serological studies.

Dr. M. L. Furcolow of the United States Public Health Service, Kansas City, Kansas, performed the histoplasmin and blastomycin complement fixation tests and supplied the blastomycin for skin testing.

The histoplasmin skin reagent was supplied by Dr. J. C. Peterson of Vanderbilt University, Nashville, Tennessee.

It is a pleasure to express my deep appreciation to these workers for their cordial cooperation.

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A CORRELATED STUDY OF TUBERCULIN, HISTOPLASMIN AND COCCIDIOIDIN SENSITIVITIES WITH PULMONARY CALCIFICATIONS IN THE ROCKY MOUNTAIN AREA[1,2]

W. K. ABSHER AND F. CLINE, JR.

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INTRODUCTION

During and since the years of World War II, rather extensive investigative studies have been undertaken concerning the etiologic factors responsible for multiple pulmonary calcifications. The results have cast doubt upon the earlier concept that all multiple lung and hilar calcifications are tuberculous in origin. It now appears that fungus infections may play a significant role in the production of these calcifications and a considerable number of cases have been shown to be associated with histoplasmin skin sensitivity. The chronological development of this subject has been thoroughly reviewed during the past few years by several authors (1, 2, 3, 11, 12) and its repetition seems hardly necessary at this time.

One of the most significant contributions has been that of Sontag and Allen (13) in their study of Ohio school children. These observers noted the presence of soft precalcific infiltrates in histoplasmin reactors and found the characteristics of these infiltrates to be similar in every detail to those of tuberculous lesions.

It follows then that physicians should be keenly cognizant of these observations lest they err in their evaluation of such pulmonary lesions. These implications are especially important today with the mass roentgenographic screening of population groups, projects which will undoubtedly uncover increasing numbers of nontuberculous lesions.

The above studies suggest that a condition such as nonfatal Histoplasma capsulatum infection may exist; however, all investigators stress the fact that this entity occurs only in a relatively small endemic section of the country, namely, the East Central States. Ferebee (5) has recently commented that in some geographic areas such as Colorado it is rare to find a native who reacts to histoplasmin. Therefore, on first thought it would appear that the problem is of no practical concern to the physician of the Rocky Mountain Area. The fallacy of such thinking, however, was quickly and forcibly illustrated to the writers when they were confronted with a case (16) diagnosed roentgenographically as active minimal pulmonary tuberculosis.

Briefly, this patient came from Dayton, Ohio (in the endemic area). His skin reactions were repeatedly negative to purified proteid derivative (PPD), 0.0005

[1] From the Tuberculosis Section, Medical and Radiological Services, Veterans Administration Hospital, Fort Logan, Colorado.

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mg., and the reaction to histoplasmin was positive. Many specimens of sputum and gastric washings were negative for tubercle bacilli by culture and guinea pig inoculation. Obviously, this individual had to be considered as nontuberculous and, in all likelihood, represented a case of subclinical histoplasmosis.

Following this experience, a cursory review of the admissions to Fort Logan revealed the fact that relatively few veterans were natives of Colorado and that a large number had lived most of their lives in the endemic area of the East Central States. A review of the personnel working in the Veterans Administration Regional Office in Denver brought out the same surprising fact. Accordingly, it was decided to conduct a survey of 1,000 veterans and Veterans Administration personnel in the Rocky Mountain Area relative to the problem of pulmonary fungus infections.

METHODS

Each subject was skin tested with purified protein derivative (PPD), 0.0005 mg., coccidioidin in a dilution of 1:100, and histoplasmin in a dilution of 1:100. The results of these skin tests were correlated with a chest roentgenogram in every instance. All skin tests were interpreted by the same group of investigators and all roentgenograms were interpreted by one radiologist who did not know the results of the skin tests. The usual standards were adopted in the interpretation of the skin reactions. In interpreting the roentgenograms, at least 10 calcifications were required before the term "multiple pulmonary calcifications" was applied to an individual case.

RESULTS

Of the 1,000 cases tested, 55.8 per cent reacted to tuberculin, 6.5 per cent reacted to coccidioidin, and 22.6 per cent reacted to histoplasmin (table 1). It will be readily noted that the percentage positive to tuberculin is similar to the findings in other parts of the country. The percentage of reactors to coccidioidin was low, as originally expected. Surprisingly enough, however, the percentage of reactors to histoplasmin was considerably higher than was anticipated, since Palmer (10) in his study obtained only 4 positive reactions in 460 Colorado nurses.

As was expected, many individuals reacted to more than one antigen (table 2). The points of interest here are that 348 (34.8 per cent) of those tested did not react to any antigen and, of this number, only one revealed multiple pulmonary calcifications on roentgenographic examination. Thirty subjects (3 per cent) reacted to all three antigens and, of this group, 5 showed multiple pulmonary calcifications. The largest group was that which reacted to tuberculin alone, and of this group only 14 revealed pulmonary calcifications. One hundred ten, or 11 per cent, reacted to both tuberculin and histoplasmin and in this group 16 showed multiple pulmonary calcifications. Of 73 reactors to histoplasmin alone, 8 showed pulmonary calcifications.

Thus, the tuberculin- and histoplasmin-positive group (T+ H+ C−) showed a higher percentage of pulmonary calcifications than any other group except the

one with positive reactions to all three antigens (T+ H+ C+). In other words, as far as this study is concerned, neither tuberculosis nor histoplasmosis has played a dominant role in the production of pulmonary calcifications.

Of this group of 1,000 cases, only 322 could be classified as native Coloradians; that is, they had spent five-sixths of their lives within the state of Colorado (Palmer's criterion (10) in his original geographic survey). The significant feature is that 40 (12.4 per cent) of these so classified natives reacted to histoplasmin. This is considerably lower than the figure for the group as a whole, which was

TABLE 1

Positive Reactions to Antigens in Survey of 1,000 Subjects

	NUMBER OF POSITIVE REACTORS	PER CENT POSITIVE
Tuberculin (0.0005 mg. PPD)	558	55.8
Histoplasmin 1:100	226	22.6
Coccidioidin 1:100	65	6.5

TABLE 2

Results of Skin Tests in 1,000 Subjects

	NUMBER OF CASES	PER CENT OF CASES
T+ H− C−	404	40.4
T− H− C−	348	34.8
T+ H+ C−	110	11.0
T− H+ C−	73	7.3
T+ H+ C+	30	3.0
T+ H− C+	14	1.4
T− H+ C+	13	1.3
T− H− C+	8	.8

T = Purified Protein Derivative, 0.0005 mg.
H = Histoplasmin, 1:100.
C = Coccidioidin, 1:100.

22.6 per cent, but is much higher than Palmer's (10) original figure of less than 1 per cent for Colorado nurses. A more detailed study of the geographic history of these 40 individuals in the present series, however, revealed that 27 had lived for one or more years within the endemic area of the East Central states. Thus their reaction to histoplasmin could possibly be accounted for by residence in other states and only 13 (4 per cent) remained unexplained on a geographic basis.

DISCUSSION

This roentgenographic and skin testing survey of 1,000 cases has served to confirm fully the previous findings of the U. S. Public Health Service investigators (1, 5, 6, 7, 8, 10), namely, that the Rocky Mountain region is not an endemic area for the so-called benign type of histoplasmosis. Nevertheless, the large

number of migrants to this area, together with those native Coloradans who spent some time in the endemic area of the East Central states during the war years, make the problem an important one to the physician in the Rocky Mountain region. This fact has been adequately demonstrated by the erroneously diagnosed case (16) presented previously.

In their recent article concerning the problem of pulmonary infiltrates associated with histoplasmin sensitivity, Furcolow (7) and his associates in Kansas City implied that a specific type of calcification was characteristic. They referred to a so-called "halo" type of calcification in which a soft areola surrounded

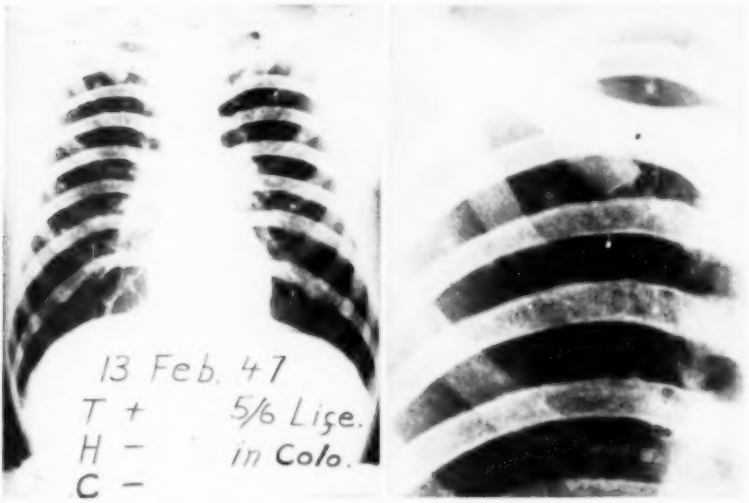

FIG. 1. (Left) Chest roentgenogram revealing multiple pulmonary calcifications in a tuberculin-positive, histoplasmin-negative individual (See figure 2).

FIG. 2. (Right) An enlargement of the right upper lung field of roentgenogram of figure 1 showing the lesion in the first right anterior interspace. Note the soft areola surrounding a central calcific core in this tuberculin-positive, histoplasmin-negative individual.

a central calcific core. That this so-called "halo" calcification is not limited to histoplasmin-sensitive individuals is illustrated in the roentgenograms in figures 1 and 2. The patient whose roentgenograms are presented in the figures exhibited a marked reaction to PPD (0.0005 mg.) and did not react to either histoplasmin or coccidioidin.

Recently Edwards and her associates (4), in reviewing the roentgenographic findings among student nurses, pointed out that calcifications associated with histoplasmin sensitivity were scattered bilaterally, involving both upper and lower lobes. In contrast, tuberculin-positive calcifications usually were limited to the upper lobes. In the present series of cases, however, no diagnostic pattern of pulmonary calcifications was noted in either the tuberculin-positive or the histoplasmin-positive group.

An additional observation in this series was that hilar calcifications, parenchymal calcifications (less than 10), or combinations of the two, occurred in 24 individuals who did not react to any of the three antigens. Long (9) has observed that, of 2,490 cases, 11 per cent lost their sensitivity to tuberculin during a ten year period. Thus there exists the possibility that sensitivity to histoplasmin and coccidioidin may behave in a similar manner. Evaluation of these 24 nonreactors who revealed evidence of previous pulmonary disease is difficult. It would appear to be the consensus of opinion that, from a diagnostic viewpoint at least, a negative tuberculin test rules out the existence of tuberculosis. Woodruff (15) has stated, "A patient anergic to tuberculin, who is not acutely ill, almost certainly does not have clinical tuberculosis." Sweany (14) has remarked, "The absence of tuberculous disease is almost certain in uncomplicated cases negative to 1:1,000 dilution of OT."

Physical examination of these 24 nonreactors revealed no evidence of other diseases, conditions, or metabolic disturbances which, according to Riley (12), are also capable of producing pulmonic calcifications.

With these facts at hand, it would seem that serious consideration should be given to the possibility that there exists yet another unrecognized causative agent or factor capable of producing hilar and/or parenchymal calcifications.

SUMMARY

1. A roentgenographic and skin testing survey of 1,000 cases from the Rocky Mountain Area relative to the problem of multiple pulmonary calcifications has been reported.

2. The survey revealed that 404 (40.4 per cent) of the individuals tested reacted to tuberculin alone and, of these, 14 showed multiple pulmonary calcifications; 73 (7.3 per cent) reacted to histoplasmin alone, of whom 8 showed multiple pulmonary calcifications; 110 (11 per cent) reacted to both histoplasmin and tuberculin, and in this group 16 showed multiple pulmonary calcifications.

3. Twenty-four cases of hilar and/or parenchymal calcifications were noted in individuals reacting negatively to all antigens.

4. Observations in the survey confirm the findings of the U. S. Public Health Service investigators, namely, that the Rocky Mountain Area is not endemic for the so-called benign histoplasmosis.

5. In this series, no diagnostic pattern or distribution of pulmonary calcifications was noted in either tuberculin-positive or histoplasmin-positive individuals.

6. The fact that "halo" type pulmonary calcifications are not limited to histoplasmin-sensitive individuals was noted.

SUMARIO

Estudio Correlativo de las Sensibilidades a la Tuberculina, la Histoplasmina y la Coccidioidina con las Calcificaciones Pulmonares en la Región de las Montañas Rocosas

1. Este estudio radiográfico y cutirreactor comprendió 1,000 personas de la Zona de las Montañas Rocosas con respecto al problema de las calcificaciones pulmonares múltiples.

2. La encuesta reveló que 404 (40.4 por ciento) de los individuos comprobados sólo reaccionaban a la tuberculina, y de ellos, 14 revelaron calcificaciones pulmonares múltiples; 73 (7.3 por ciento) sólo reaccionaron a la histoplasmina, y 8 de ellos mostraron calcificaciones pulmonares múltiples; 110 (11 por ciento) reaccionaron tanto a la histoplasmina como la tuberculina, y 16 de este grupo revelaron dichas calcificaciones.

3. En sujetos negativos a todos los antígenos notáronse 24 casos de calcificaciones hiliares y/o parenquimatosas.

4. Las observaciones realizadas en eta encuesta confirman los hallazgos obtenidos por el Servicio de Sanidad Pública de los E. U. A., o sea, que la región de las Montañas Rocosas no es endémica para la llamada histoplasmosis benigna.

5. En esta serie no se observó ningún patrón o distribución de calcificaciones pulmonares utilizable para diagnóstico, ni en los positivos a la tuberculina ni en los positivos a la histoplasmina.

6. Se notó que las calcificaciones pulmonares en "halo" no se limitaban a los individuos histoplasmino-sensibles.

Acknowledgements

The cooperating physicians at the Veterans Administration Hospital, Fort Logan, Colorado, and the Veterans Administration Regional Office in Denver, Colorado, who aided in performing the skin tests in this series, were Drs. W. L. Craddock, W. A. Hines, and H. S. Zuckerman. The project was performed under the supervision of Dr. D. W. Zahn, Chief of the Tuberculosis Section.

The coccidioidin was supplied by Dr. Charles E. Smith of Stanford University, Palo Alto, California.

The histoplasmin was supplied by Dr. J. C. Peterson of Vanderbilt University, Nashville, Tennessee.

Bacteriologic studies were performed by Mr. E. A. Brosbe under the supervision of Dr. Wray J. Tomlinson, Chief of Laboratory Service, Veterans Administration Hospital, Fort Logan, Colorado.

The authors desire to express their sincere appreciation to these workers for their assistance in this study.

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TUBERCULOUS PERICARDITIS[1]

Report of a Case With a Ten Year Follow-up

SIDNEY KREININ AND JAMES ALLEN COOLEY

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INTRODUCTION

Complete recovery from tuberculous pericarditis with effusion is sufficiently unusual to warrant the reporting of a single case.

Tuberculous pericarditis carries with it a mortality sufficiently high to question recovery in any given case. There appeared in the American medical literature in the ten years from 1937 to 1947 nine reports (1, 4, 6, 7, 8, 9, 10, 11 and 13) of individual cases of tuberculous pericarditis, and five series of cases (2, 3, 4, 5 and 14).

All of the 9 reported cases died. Hodges (4) found 5 cases in the records of the Norfolk General Hospital between the years 1923 and 1937, all of whom died. Of Keefer's (2) 20 cases, 18 died. Fenger and Hansen (14) collected 6 cases from the files of the Glen Lake Sanitarium, of whom 3 died. Four of Blalock and Levy's (5) 20 cases were alive at the time of writing (1937) but one of those was dying. Harvey and Whitehall (3) collected 95 cases from the records of the Johns Hopkins Hospital dating back to 1899. Of this series, 20 were cases of tuberculous pericarditis with effusion, of whom 16 died.

The aphorism that tuberculosis of the pleura and peritoneum is most often seen under forty years of age while tuberculosis of the pericardium is most often seen in those over forty years (2) of age must be modified in the light of recent findings.

Bellet *et al.* (12) found that tuberculous pericarditis occurred most often in children and young adults while half of Fenger and Hansen's (14) cases occurred between the ages of 20 to 40. Harvey (2) states that the disease is found in every decade of life.

It is generally agreed that the great preponderance of cases occurs in the Negro race. Of the 9 collected cases, 6 (1, 4, 6, 7, 11 and 14) were Negroes. In Harvey and Whitehall's (2) series of 20 cases, 15 were Negro.

Primary tuberculosis of the pericardium is extremely rare if not highly improbable (10). Tuberculous pericarditis is always secondary to some other tuberculous lesion (3). Tuberculosis of the pericardium arises from an invasion of tubercle bacilli from mediastinal lymph, the lungs, the pleura, or the peritoneum.

The condition is not always recognized except where massive effusion exists. In a series of 1,292 autopsies, Fenger and Hansen (14) found 22 cases of proved tuberculous pericarditis; 16 cases diagnosed at autopsy were not clinically diag-

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nosed. They conclude that tuberculous pericarditis is a rare complication of tuberculosis and carries a grave prognosis.

Keefer (2) subdivided his cases into the following groups:

(*1*) patients with symptoms and signs of a wasting disease and obscure fever;
(*2*) patients with symptoms and signs suggesting congestive heart failure;
(*3*) patients with symptoms and signs of multiple serous membrane tuberculosis;
(*4*) patients with symptoms and signs of massive pericardial effusion; and
(*5*) patients with symptoms and signs of miliary tuberculosis.

The course of the disease runs in three stages (10): sero fibrinous exudate; pericardial thickening and effusion; and the development of extensive adhesions confining the expansion of the heart. The average duration of the disease from the onset of symptoms until termination was three months (two to four months in Keefer's series (2) and three and seven-tenths months in Harvey and Whitehall's (3) series).

The poor prognosis in the older patients is associated with the inability of the cardiovascular system to cope with its added burden, while in the younger cases the frequency of development of other serious tuberculous lesions is responsible (3).

Especially in young people, tuberculous pericarditis with effusion must be differentiated from rheumatic pericarditis with effusion. Bellet *et al.* (12) noted the importance of finding the tubercle bacillus in the pericardial fluid, the absence of cardiac murmurs, and the demonstration of a small heart after the production of a pneumopericardium.

The following case is reported as it represents an apparently complete recovery from tuberculous pericarditis with effusion.

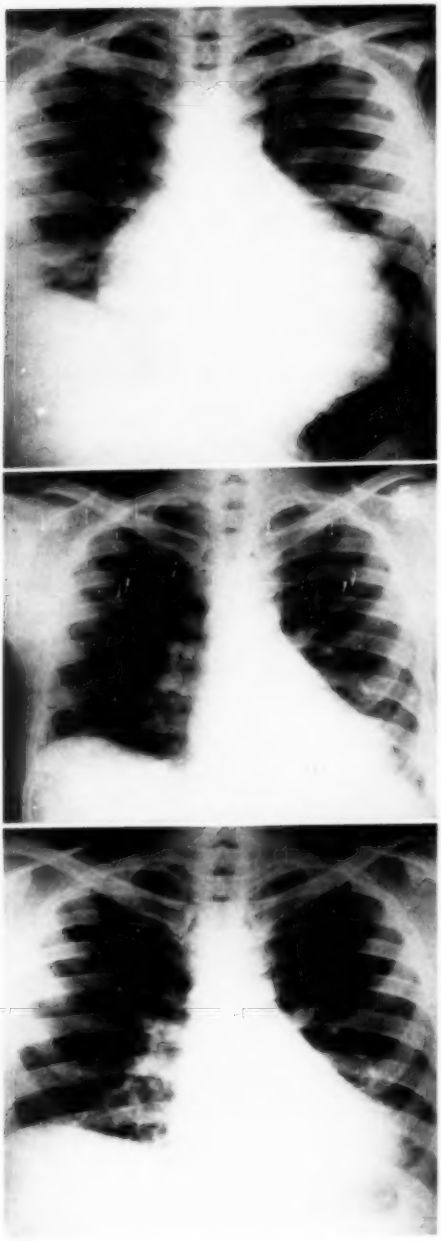
CASE REPORT

W. M., an 18 year old white male, was admitted to the Swedish Hospital (service of the late Dr. James Pullman) on August 4, 1936 complaining of pain in the chest and left shoulder, fever, and sweating.

In March, 1936 the patient had had a right pleural effusion. He was in bed for three weeks during which time his chest was tapped by one of us (J. A. C.) and about 2,000 cc. of fluid removed.

On July 29 the patient complained of suprasternal pain. He remained at home for the next two days, but on August 1 he went to the beach. The next day he complained of pain in the left chest which radiated to the axilla and the left shoulder. On August 4, because of an increase in the severity of the pain, fever, and rapid pulse he was hospitalized. Physical examination on admission to the hospital revealed an acutely ill young white male with a temperature of 104°F., a pulse rate of 130 and respirations of 40 per minute. On percussion the left anterior chest was dull from the third rib to the base. In the axilla the dullness merged with cardiac dullness. The breath sounds were diminished. The right chest was dull on percussion from the sixth rib to the base with diminished breath sounds. Posteriorly the left chest was dull at the base with diminished breath sounds. The right chest was flat posteriorly with absent breath sounds.

The left border of the heart could not be outlined by percussion as it merged with axillary dullness. The cardiohepatic angle was not diminished. Over the precordium the heart sounds were diminished and were best heard over the fourth costochondral junction. A systolic murmur was present.



Roentgenographic examination on the day of admission revealed that the trachea was in the midline and the heart enlarged in both borders. A pericardial effusion was present. The left diaphragm and the left lung were normal. The right diaphragm was not well outlined. There was an effusion of the right lower pleural cavity but the right lung was normal.

On admission the erythrocytes were 4,500,000 per cu. mm., the hemoglobin was 75 per cent of normal, the total leukocyte count was 11,700 per cu. mm. with 87 per cent neutrophils. Examination of the urine revealed no abnormalities.

During the next few days the patient's condition remained unchanged. Morphine was given for pain and restlessness. He became cyanotic though dyspnea was moderate. On August 5, a friction rub was heard over the fourth left costochrondral junction. The following day cyanosis was marked and there was some precordial pain. His pulse was irregular and of small volume. The friction rub was now heard over the entire precordium. There was slight venous distention, especially of the jugular veins. The dullness in the left axilla had diminished while the findings in the right chest were unchanged. A pericardial paracentesis was done and 225 cc. of serosanguineous fluid were removed.

During the next five days the patient remained seriously ill with fever (104°F.), auricular fibrillation, venous distension, cyanosis, and dyspnea. Six hundred cc. of straw-colored fluid were removed from the pericardial cavity on August eleventh. Examination of smear of the fluid was negative for acid-fast bacilli. A guinea pig was inoculated with the fluid. On October 10 the guinea pig was opened and examined by Dr. Leo Meyer. He reported

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FIG. 1. Chest roentgenogram taken August 3, 1936. The cardiac shadow is markedly enlarged in all directions. It has lost its normal border contours and has a configuration characteristic of pericardial effusion. There also is an effusion in the right pleural space, fluid reaching up to the level of the fourth rib and axilla, separating the parietal and visceral pleura and extending into the interlobar fissure between the right lower and middle lobes. The outer third of the right diaphragm is elevated and fixed.

FIG. 2. Roentgenogram obtained on October 7, 1944 shows that the cardiac contour has decreased greatly in size. The protrusion of the right cardiac border is gone. The right cardiac contour is normal. The left cardiac border still shows some elongation, as by a fixed pericardiopleural or mediastinopleural adhesive pleurisy, but the total size of the heart shadow has returned to approximately normal. The right diaphragm remains elevated and fixed in its outer margin. The right parietovisceral pleura are separated and thickened. There also are some fibro-proliferative changes now evident in the left lower lung field.

FIG. 3. Roentgenographic examination of the heart and lungs (December 1, 1947) in the postero-anterior, lateral and right and left oblique projections shows the following findings:

The cardiac shadow shows elongation of its left border in the oblique projections. There is an obliterative adhesive pleurisy involving the right diaphragm and the right axillary area. The parietovisceral pleural space in each axilla has been obliterated. The right diaphragm is elevated and fixed in its outer third. The left diaphragm is also partially fixed. There are dense basilar mediastinal pleural adhesions and there is a thickening and irregular calcification of the pleura postero-laterally in the lower third of the left chest. The parietovisceral space in the left chest has been obliterated by thickening of the pleura.

In view of the history of a previous tuberculous pleurisy, mediastinitis and pericarditis, these diffuse thickenings of the pleura probably represent the obliterative end stage of a tuberculous pleurisy. The calcific deposit within the pleura further bears this out. Judging by the present findings, the process has involved the pleural areas in each hemi-thorax, the mediastinal pleura and the pericardial pleura.

There is no evidence of parenchymal tuberculous deposit other than an occasional small, well-calcified primary focus.

"The inguinal glands were enlarged and caseous. Direct smear of the necrotic tissue discloses the presence of numerous acid-fast bacilli."

During the next two weeks the patient remained critically ill with considerable evidences of cardiac insufficiency. The pericardial fluid reaccumulated so rapidly during this period that it was necessary to remove 400 to 1,700 cc. on four separate occasions.

Gradual improvement was apparent, however, and by August 28 the patient was quite comfortable, although still seriously ill. There was no cyanosis or venous engorgement. His respirations were 30 per minute but his pulse still ranged about 130 per minute. Anteriorly there was flatness over the third rib merging with cardiac dullness. Examination of the chest on September 6 was as follows: The flatness over the left rib merged with cardiac dullness; the left axilla was resonant and breath sounds were heard; posteriorly there was impaired resonance from the sixth rib to the base, tubular breathing was present over this area; the heart rate was 110 per minute; there was evidence of pericardial fluid. By the 9th of September the area of dullness over the anterior left chest was smaller. The left axilla was completely resonant. There was no friction. Voice sounds were increased over the posterior chest. Two days later his pulse continued out of proportion to his temperature and was 130 per minute. However, his color was good and respirations were easy and normal. There was still evidence of pericardial fluid.

On September 21 the Mantoux test was negative. Improvement continued throughout the month and by October 30 his pulse was 86 per minute and it was possible to discontinue the digitalis.

The report of a chest roentgenogram obtained on October 31 read as follows: "The trachea is in midline; the base of the heart is enlarged; cardiac silhouette is greater than normal but not as great as on previous examinatjon. I believe if any effusion is present in the pericardium the amount is small. There is some congestion at the right base with a very small amount of fluid in the left costophrenic area. Lungs show no definite indication of tuberculosis."

The patient was discharged on October 31, 1936 and remained at home in bed until February 15, 1938. During this fifteen and one-half month period the patient took his pulse daily and refused to leave his bed. Around February 15 he got out of bed for about an hour, took his pulse, was dissatisfied and returned to bed for three weeks. He then left his bed for short periods at a time, gradually increasing his stay out of bed. On October 15, 1938 he left the house for the first time. In November he played nine holes of golf and when he noted that his pulse quickened he returned to bed for a week. He returned to school at the end of 1938 and was graduated at the end of 1942. On six occasions he was called and examined by his draft board. At first his history was sufficient for rejection but, since the lad appeared so well and since physical examination revealed nothing, the hospital record was requested and a note signed by one of us (J. A. C.), certifying to the above illness, was sufficient to keep him from service. In 1946 he married.

From 1938 to date he has been seen by us for mild upper respiratory infections on about eight occasions. His chest has remained clear and there has been no sign of pericardial involvement or any other evidence of tuberculosis.

Acknowledgment

The writers wish to express their thanks to Dr. Alexander Sarafianos, who performed the pericardial taps.

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STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS PERICARDITIS[1]

Report of Three Cases

RICHARD P. JOHNSON AND BERNARD A. BERCU

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INTRODUCTION

Tuberculous pericarditis is a very serious disease. In the 37 proved cases reported by Harvey and Whitehill (1) in 1937 from the Johns Hopkins Hospital there was an 83 per cent mortality, most of the cases dying within months of the onset of symptoms. Some (2) have stressed the occurrence of the disease in elderly males, and a few reports (3, 4) are to be found describing cases exclusively in males over 50 years of age. This, however, is not unique and might even happen in pulmonary tuberculosis. The Negro race is especially susceptible, particularly the age group 15 to 30 years which constitutes the majority of cases in some reported series (1, 5).

There is much discussion in the literature about "primary" tuberculous pericarditis (6). This term may be used in one of two senses. (*1*) "Clinically primary" tuberculous pericarditis (7, 8) means that the pericarditis is the patient's principal illness; it is the presenting disease and is the cause of his seeking medical aid. He may, in addition have demonstrable tuberculosis elsewhere. (*2*) The term "anatomically primary" tuberculous pericarditis means that tuberculosis is to be found only in the pericardium (3, 9). Some deny the existence of this form. The question is academic, however, for it would not be anticipated that the disease would originate in the pericardium. Tuberculosis may reach the pericardium by several routes. Most frequently the source of infection is from caseous mediastinal nodes lying in close proximity to the pericardium. Less frequently the disease is due to direct extension from tuberculosis of the pleura or lung, and still less common is hematogenous seeding of the pericardium.

The treatment of tuberculous pericarditis has been symptomatic, covering all that is implied in a sanatorium regimen. Pericardial tapping is done as necessary to relieve cardiac tamponade. To tap the pericardium and replace the fluid by air when tamponade is not present has been recommended by those who believe this may result in quicker recovery, or at least recovery without adhesions and without the possibility of a later chronic constrictive pericarditis. This assumption is still without proof. To the writers' knowledge there are only two reports in the literature on the use of streptomycin in tuberculous pericarditis. One report (10) concerned a 19 year old Negro girl who developed an acute pericardial effusion during the third month of a rapidly progressing tuberculosis of lymph nodes. Tubercle bacilli were cultured from the pericardial fluid. There was immediate improvement with the use of streptomycin (3 Gm. daily for 120 days)

[1] From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

as shown by the complete disappearance of symptoms, and the cardiac silhouette decreased in size. Eleven months after streptomycin treatment the patient was still asymptomatic, had negative cultures, and was ambulatory at home. The cardiac silhouette was still slightly larger than normal. Meredith (11) reports the case of a Negro male aged 17 years who was febrile and had proved tuberculosis of the lymph nodes. A large pericardial effusion was tapped but tubercle bacilli were not recovered. After streptomycin was started (200 mg. every three hours for 33 days) there was marked improvement. The patient became afebrile, gained weight, and the cardiac silhouette decreased in size. Three months after streptomycin therapy the patient was feeling very well, although he was still in a sanatorium for treatment of his pulmonary tuberculosis.

The present report is concerned with 3 patients with tuberculous pericarditis who received streptomycin as part of their treatment.

The first case is that of a middle aged white male physician who had an acute tuberculous pericardial effusion followed in a few months by chronic constrictive pericarditis for which he was surgically treated. One year later he was in excellent health. The other two cases are of Negro youths. One (case 2) made a clinical recovery but there persists a markedly thickened, though asymptomatic, pericardium. The other patient (case 3) developed a pericardial effusion which later completely reabsorbed without apparent significant residual except for an abnormal electrocardiogram. The amounts of streptomycin used in the three cases were: 7.5 Gm. in 13 days; 120 Gm. in 120 days; and 42 Gm. in 42 days, respectively. In cases 1 and 2 tubercle bacilli were cultured from the pericardial fluid. In case 3 no aspiration was done and therefore the diagnosis of tuberculous pericarditis, though probable, was not proved. None of these patients showed any toxic symptoms from the streptomycin treatment.

CASE REPORTS

Case 1: A regular army physician, 59 years of age, suddenly became ill in October, 1945 with malaise, fever, and weakness following a mild upper respiratory infection. The diagnosis was left basal pneumonia. In two weeks he was afebrile and ambulatory but after three days his fever recurred. Penicillin and sulfonamides were now without benefit. In December, 1945 he was admitted to Letterman General Hospital where a diagnosis of pericardial effusion was made on the basis of increased cardiac dullness, faint heart sounds, distended jugular veins, and a liver enlarged downwards 3 cm. below the right costal margin. Paradoxical pulse was present, blood pressure was 120 systolic and 80 diastolic, venous pressure (antecubital) 177 mm. water. The total leukocyte count was 10,000 per cu. mm. with 74 per cent segmented cells. His pericardial sac was tapped and straw-colored fluid removed, which showed a few white blood cells but no organisms on smear, a specific gravity of 1.032, and 5.5 Gm. of protein per 100 cc. On January 25 this pericardial fluid was reported positive for tubercle bacilli on culture and guinea pig inoculation.

Beginning on February 2, he was given 0.1 Gm. streptomycin intramuscularly every four hours for a total of 7.5 Gm. This was followed by a decrease in the amount of pericardial fluid, a drop in the erythrocyte sedimentation rate from a high of 95 mm. in one hour to 12 mm. by March, 1946, and a drop in venous pressure from 177 mm. to 120 mm. of water, with improvement in his general health. Search for other manifestations of tuberculosis showed that the patient had been hospitalized in 1942 because of a chronic cough of four years duration. Mild hypertension and arteriosclerosis were found, and in

addition, a markedly thickened and calcified left pleura with some nodose fibrous lesions in the left apex. The diagnosis at that time was arrested pulmonary tuberculosis, and the patient was returned to limited duty.

On March 29, 1946 he was transferred to Moore General Hospital because of his pericardial and pulmonary tuberculosis. He very soon developed marked enlargement of the liver, ascites, peripheral edema, and rales in the bases of both lungs. A diagnosis of chronic constrictive pericarditis was made and he was sent to Fitzsimons General Hospital in May for surgical treatment. Here all the evidence necessary for this diagnosis was confirmed: distended neck veins showing inspiratory filling; distant heart sound; pulsus paradoxicus; ascites; a nontender liver palpable four fingerbreadths below the right costal margin; and a venous pressure (antecubital) of 180 mm. water. Electrocardiograms were available for the period prior to this illness, and they were normal. Tracing of December 4, 1945 showed a lowered amplitude of QRS and T in all leads taken: I, II, III and CF4. By December 31 there was asymmetrical inversion of T in leads I, II, III and a diphasic T in CF4.

The preliminary treatment consisted of a low salt diet, digitalis, and mercurial diuretics. He showed temporary improvement, but after August, 1946 he became worse and his ascites increased. In January, 1947 a pericardiectomy was done and 7 thick pieces of laminated fibrous tissue were removed with immediate improvement of cardiac function. Histological study of the excised material showed a relatively acellular dense fibrous tissue with discrete granulomatous nodules containing either epithelioid cells, lymphocytes and an occasional Langhans' giant cell, or relatively acellular encapsulated organizing caseous foci. No acid-fast bacilli were demonstrated.

Following the operation, the patient improved but it was one year before ascites and edema of the legs were fully controlled. His electrocardiogram remained abnormal. The patient was in fine condition July, 1948 having made an apparently complete recovery.

Case 2: A 20 year old Negro soldier was admitted to William Beaumont General Hospital in December, 1946 stating that he had been well until one week previously when he noted the onset of malaise, a nonproductive hacking cough, and a constant dull ache in the left scapular region which was not aggravated by deep breathing or coughing. He then developed a sharp pain over the right chest anteriorly that was aggravated by deep breathing and coughing. The patient had been working as a butcher and laborer in an army hospital for the previous eleven months. His past and family history were noncontributory and there was no known exposure to tuberculosis.

Physical examination on admission to the hospital revealed that he was well developed and well nourished, and he appeared acutely ill. His blood pressure was 120 systolic and 80 diastolic. Examination of the heart revealed that the apex beat was diffuse and the left border of dullness on percussion was on the anterior axillary line in the fifth intercostal space. A soft systolic murmur was heard in the left third interspace close to the sternum. The second pulmonic sound was reduplicated and the rhythm was normal. The remainder of the physical examination was negative. Laboratory data on admission were as follows: total leukocyte count 6,500 per cu. mm. with 45 per cent segmented neutrophils, 9 per cent band cells, 43 per cent lymphocytes, and 3 per cent eosinophils. The hemoglobin concentration was 15.6 Gm. per 100 cc. Urinalysis was normal and the specific gravity was 1.020. A serologic test for syphilis (Kahn) was negative.

For the first two weeks the patient presented mainly a febrile course, with temperatures ranging from a low of 100°F. to a high of 103°F., spiking daily in the afternoon. The pulse averaged 90 to 100 per minute. He complained mainly of headaches. On December 17, fluoroscopy revealed an enlarged cardiac shadow and an electrocardiogram showed slight elevation of the ST segments in leads I, II, III and CF4 (figure 3). On December 21, a pericardial friction rub was heard and an electrocardiogram showed inversion of T in leads I, II and CF4. By December 26, the pericardial fluid had increased and the heart tones were of poor intensity. The erythrocyte sedimentation rate was 38 mm. in one hour.

On February 3, 1947 a pericardial tap was done with the removal of 100 cc. of dark straw-

colored fluid. From this tubercle bacilli were cultured, but they were nonpathogenic for a guinea pig. Smear of the fluid sediment was negative. On February 17, the patient was drowsy, weak and confused. Cerebrospinal fluid examination was normal and neurological examination revealed a horizontal nystagmus with the fast component to the left. However, the patient was alert by February 22, and no definite cause for the episode was found, though it may have been salicylism. During this period albuminuria appeared and it persisted throughout his hospitalization. A second pericardial tap on March 1, yielded 250 cc. of dark amber fluid from which tubercle bacilli were again cultured which were still nonpathogenic for the guinea pig. The patient continued to have a remittent and intermittent fever up to 102°F. with a pulse rate of 90 to 100 per minute. His abdomen was slightly distended and "doughy" on palpation. On March 3, 1947 a chest roentgenogram revealed a small amount of fluid in both costophrenic angles. There was a gradual increase in the right pleural effusion and a thoracentesis was done on that side, with the removal of 330 cc. of straw colored fluid. No organisms were recovered on culture or guinea pig inoculation.

Sputum examinations for tubercle bacilli and blood cultures were negative. The sedimentation rate remained elevated at around 36 mm. in one hour. Pericardial taps on March 22, June 19 and July 21 and 28 yielded from 250 to 500 cc. of turbid yellow fluid (figure 1). Cultures of these specimens revealed tubercle bacilli but all reports obtained at the time were nonpathogenic for a guinea pig. At the end of July, the total plasma proteins were 7.9 Gm. per 100 cc. (albumin 2.8, globulin 5.1). There was no peripheral edema, the liver was not palpable, but the venous pressure (antecubital) was 230 mm. of water. The patient was given several injections of concentrated serum albumin. His temperature gradually fell over a period of several months and by September, 1947 he was having only occasional elevations to 100°F.

Because of the diagnosis of tuberculous pericarditis, the patient was transferred to Fitzsimons General Hospital on October 8, 1947 for further study. Examination at that time revealed signs of fluid in both lung bases, and a friction rub was heard over the entire precordium. On October 14, the patient was dyspneic and cyanotic and he complained of pain in the left anterior chest. The liver was palpable for the first time, four fingerbreadths below the right costal margin, and was tender. By October 17, there was pitting edema of both legs up to the knees and definite evidence of ascites. Venous pressure (antecubital) was 150 mm. of water, decholin time was 19 seconds, and ether time, 7 seconds. The patient was treated with mercupurin with loss of the edema.

On October 27, he was started on streptomycin, 0.5 Gm. intramuscularly every twelve hours, to be continued for 120 days. From this time on, the patient remained afebrile and his pulse ranged from 80 to 90 per minute. Erythrocyte sedimentation rates remained about 25 mm. in one hour. Total plasma proteins were 8.5 Gm. per 100 cc. (albumin 2.7 globulin 5.8). The patient had no edema or ascites by the middle of November. At this time a report was received on pericardial fluid removed on August 20 at William Beaumont General Hospital stating that it was positive for tubercle bacilli which were pathogenic for a guinea pig. Numerous gastric washings and urine cultures were negative for tubercle bacilli. White blood cell counts remained normal. On December 5, venous pressure (antecubital) was 135 mm. water with a rise to 200 mm. on pressure over the right upper quadrant of the abdomen. Arm-to-tongue circulation time (Decholin) was 22 seconds and with ether was 12 seconds. The patient was asymptomatic and had a good appetite by the end of December. During January, 1948 he continued this same good course and the only physical findings were a false pulsus paradoxicus (present only when he held a deep inspiration), enlargement of the cardiac area, and evidence of pleural thickening over the right lower lobe. The liver could not be felt.

During the rest of the patient's hospital stay until he was transferred to a Veterans Hospital in April, 1948 he remained asymptomatic and feeling well (figure 2). It was difficult to keep him on modified bed rest. The total plasma protein was 8.6 Gm. per 100 cc. (albumin 4.4, globulin 4.2). Retrograde pyelograms and roentgenograms of bone, as well as liver

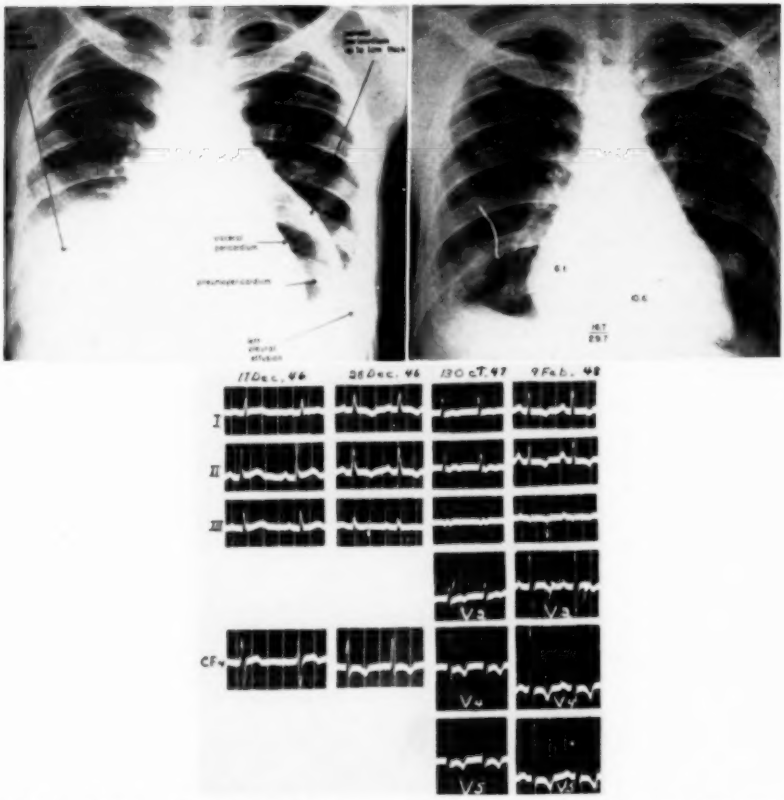

FIG. 1. Case 2. (Upper left) Chest roentgenogram of July 28, 1947, more than seven months after onset of illness, showing pericardial and bilateral pleural effusions. The air in the pericardium was injected after removal of fluid and demonstrates a greatly thickened parietal pericardium.

FIG. 2. Case 2. (Upper right) Chest roentgenogram of March 18, 1948 after the patient had been given four months of streptomycin therapy. There remains thickened pericardium and pleurae.

FIG. 3. Case 2. (Bottom) Electrocardiogram of December 17, 1946 showing slight elevation of ST segments in leads I, II, III and CF4. This is a pattern seen early in pericarditis and seldom obtained in tuberculous pericarditis. The three following tracings show the more commonly found pattern with inversion of T waves and decreased amplitude of QRS. Nodal rhythm is present in tracing of October 13, 1947; this was transient.

and kidney function tests, were normal. The false pulsus paradoxicus disappeared. Venous pressure (antecubital) was 140 mm. of water, and arm-to-tongue (Decholin) circulation time 17 seconds.[2]

[2] In January, 1949 this patient was still clinically well.

Case 3: An 18 year old Negro soldier was admitted to a station hospital in Japan on August 26, 1947, complaining of loss of weight for three months and chills for four days. The patient stated that during the past three months he had had poor appetite, lost 15 pounds in weight and felt tired. Four days before admission he began to notice chilliness at night necessitating the use of extra covering. He had a "tingling" sensation over the sternum. There was no cough or hemoptysis.

Past history was significant in that the patient had had a chancroid four months before admission which had been treated with sulfadiazine. Family history was noncontributory, and there was no history of exposure to tuberculosis.

Physical examination revealed him to be thin, poorly nourished, undersized, and he appeared chronically ill. Blood pressure was 110 systolic and 60 diastolic. The heart was not enlarged, the tones were of good quality, and no murmurs were audible. Pulse was 52 per minute with regular rhythm. The rest of the examination was negative. Laboratory data: erythrocyte count was 4.16 million per cu. mm., the hemoglobin was 100 per cent of normal, the total leukocyte count was 8,700 per cu. mm. with 60 per cent segmented neutrophils, 34 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. Erythrocyte sedimentation rate was 56 mm. in one hour. Serologic test for syphilis (Kahn) was positive. The urine was normal. Hookworm larvae and Trichuris trichuria ova were found in the stools. Examination of the blood for malarial parasites was negative. Blood cultures were sterile. A roentgenogram of the chest showed an enlarged right upper hilar lymph node and lines of increased density radiating into the first and second right anterior interspaces.

The patient had an intermittent fever with daily peaks of 103°F. He had only a feeling of malaise and complained of no pain. During the last half of September, the patient's fever became lower with daily rises to 99°F. He felt stronger and his appetite improved. The erythrocyte sedimentation rate remained about 35 mm. in one hour. The patient was treated for the hookworm and whipworm infestations with hexylresorcinol and tetrachlorethylene. On October 13, the titer of the serologic test for syphilis (Kahn) rose to 320 "units" and the patient was given 8 million units of penicillin intramuscularly over a period of ten days. Except for an initial Herxheimer reaction, the patient's fever remained low grade with rises to 99.5°F. On November 18, while the patient was sitting up, he was suddenly seized with a sharp pain in the left anterior chest which radiated to the left shoulder. There was marked dyspnea but no cough or hemoptysis. The pain disappeared spontaneously in about thirty minutes. The total leukocyte count was 5,800 cells per cu. mm. with a differential showing 9 per cent eosinophils. Sedimentation rate was 32 mm. in one hour. An electrocardiogram showed only sinus arrhythmia (figure 4). On November 19, a friction rub could be heard over the entire precordium. A soft blowing systolic murmur was heard at the apex. Chest roentgenogram revealed an increase in the size of the heart of 3 cm. in the transverse diameter. A tentative diagnosis of tuberculous pericarditis was made. The patient's temperature was now intermittent with daily spikes to 101°F. The pericardial friction rub disappeared by November 21 and the heart sounds became distant. The titer of the Kahn test dropped gradually to 40 "units". Sputum examinations for tubercle bacilli remained negative. Chest roentgenograms remained unchanged. On November 28, the patient was evacuated to the zone of the interior. On arrival in the United States and while awaiting transfer to an Army general hospital, laboratory study showed: a total leukocyte count 5,000 cells per cu. mm., hemoglobin concentration 14.8 Gm. per 100 cc., erythrocyte sedimentation rate 6 mm. in one hour, Kahn test 10 "units" and urine normal (figure 5).

On admission to Fitzsimons General Hospital January 8, 1948 the patient was asymptomatic. His temperature was normal. Physical examination revealed no abnormalities. The erythrocyte sedimentation rate was 10 mm. in one hour. A roentgenogram of the chest showed the large discrete lymph node enlargement in the right hilar region. The heart shadow was smaller but still enlarged. Lung fields were normal. Electrocardiogram showed

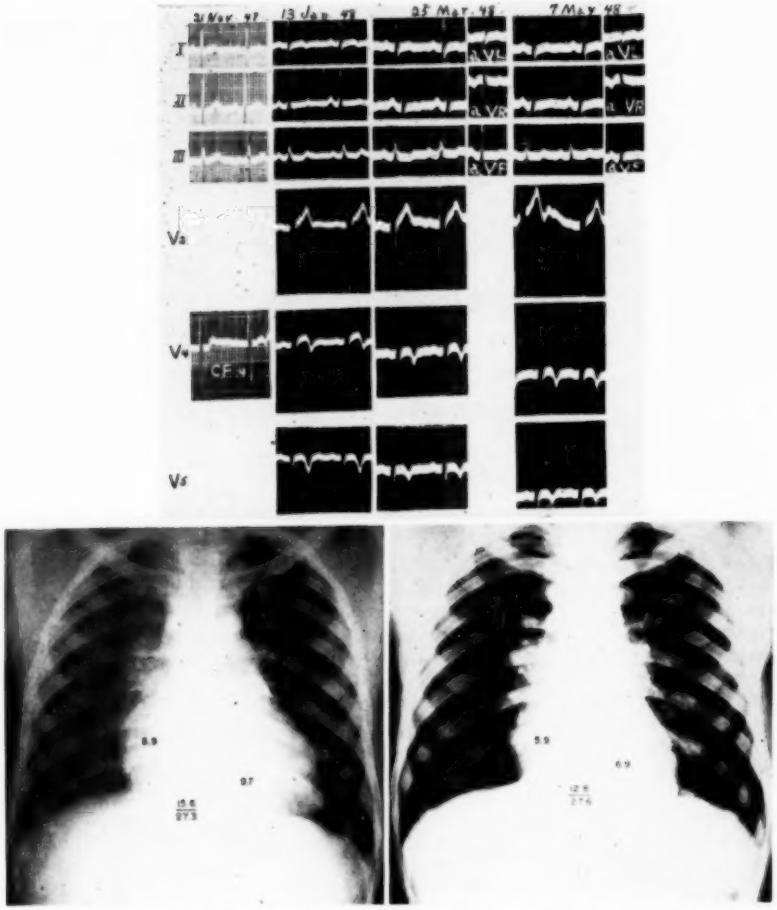

FIG. 4. CASE 3. (Top) Tracing of November 21, 1947 is essentially normal though the notching of T in CF4 may be suspicious of pericarditis. Tracing of January 13, 1948 reveals a pericarditis pattern showing inversion of T in leads I, V_4 and V_5, and decreased amplitude of T in leads II and III. In March, 1948 further changes are seen in that T in leads II and III is now inverted. Tracing of May 7, 1948 shows regressive changes in T waves of limb leads. However, the abnormal T in V_4 and V_5 persists.

FIG. 5. Case 3. (Lower left) Chest roentgenogram of December 26, 1947 showing a pericardial effusion. Note especially the enlarged (right) hilar lymph node, a common precursor of tuberculous pericarditis.

FIG. 6. Case 3. (Lower right) Chest roentgenogram of January 26, 1948 showing return of the cardiac silhouette to normal size following streptomycin therapy.

inverted T in leads I, V_4 and V_5 and was interpreted as showing a pericarditis pattern (figure 4).

Because the lymph node enlargement was considered to be tuberculous and potentially unstable, and because of the associated pericarditis, the patient was given a course of streptomycin intramuscularly, 0.5 Gm. every twelve hours for a total of 42 days. During this time the patient remained asymptomatic. He was afebrile and his total and differential leukocyte count and erythrocyte sedimentation rate remained normal. Examinations of numerous gastric washings were negative for tubercle bacilli. The serologic tests for syphilis became negative. Electrocardiograms showed some regressive changes but inversion of T persisted in leads $V_{4,5,6}$ (figure 4). A roentgenogram of the chest on January 26, 1948 showed a moderate decrease in the size of the enlarged right hilar node. The cardiac silhouette had decreased to normal size (figure 6). In July, 1948 the patient was transferred to a Veterans hospital and, at that time, he was asymptomatic, afebrile, and appeared well. Physical examination revealed no abnormalities. The only apparent abnormalities remaining were the large hilar node and the electrocardiographic evidence of pericarditis.

SUMMARY

Two cases of proved and one case of highly probable tuberculous pericarditis which responded satisfactorily to streptomycin therapy are reported.

SUMARIO

La Estreptomicina en el Tratamiento de la Pericarditis Tuberculosa

Los tres casos comunicados, dos comprobados y uno muy probable, de pericarditis tuberculosa respondieron satisfactoriamente a la estreptomicinoterapia.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS[1, 2]

III. Effect on the Pathogenesis of Early Tuberculosis in the Guinea Pig Infected with Streptomycin-sensitive H37 Rv Tubercle Bacilli

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INTRODUCTION

Up to the present time, reports of the results of streptomycin therapy in the experimental animal have dealt chiefly with therapy instituted immediately after injection with virulent tubercle bacilli, or therapy instituted after the disease was well established. This paper reports the early course of a tuberculous infection in normal guinea pigs to which streptomycin was administered prior to injection with highly virulent streptomycin-sensitive microorganisms.

It was demonstrated by Krause (1, 2), and later by others (3, 4, 5, 7), that within four to six days after subcutaneous inoculation there is a widespread dissemination of tubercle bacilli throughout the body of the guinea pig, although gross and microscopic pathological lesions may not be observed before six to ten days. Krause's findings show that, in order to prove the presence or absence of viable tubercle bacilli in early tuberculosis in the guinea pig, there should be a subinoculation of the triturated organs from an infected animal into normal guinea pigs, in addition to gross and microscopic examination of the tissues.

METHODS

In the experiment reported here, 32 tuberculin-negative male guinea pigs, each weighing about 450 Gm., were divided into two groups of 16 each, one group for treatment and one for control.

Preparation of suspension of bacilli: An evenly dispersed 14 day culture of H37 Rv microorganisms in Tween-albumin medium was diluted with physiological saline until a standard loopful of the culture spread on a slide over an area 15 by 15 mm. in size, contained 20 to 50 microorganisms per oil immersion field. The final suspension adjusted in the Klett Summerson colorimeter gave a dial reading of 17. Using this figure, it was calculated (6) that 1.0 cc. contained approximately 20,000,000 tubercle bacilli.

Therapy: The animals in both groups were injected subcutaneously in the midline, anterior to the symphysis pubis with 0.2 cc. of the suspension, which is equivalent to approximately 4,000,000 bacilli. In Group I, streptomycin therapy was begun forty-eight hours prior to infection. Each animal received 18,000 γ of the drug per day in four doses; three doses of 4,000 γ each at 7 a.m., at 12 noon, and 5:30 p.m., and the last dose of 6,000 γ at 10:30 p.m. The treatment was continued throughout the experiment.

Sacrifice periods of animals and subinoculation: Two treated and two control animals were killed at 3, 5, 10, 15, 21, 27, and 39 day intervals. Tissues from the treated animals sacrificed at 3, 5, 10, 15, and 21 days, as well as tissues from the control animals killed at 3, 5, and 10 days, were removed and studied as follows: One iliac node, half of the spleen, and two

[1] From The Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

[2] This study was aided by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

tracheobronchial nodes were removed aseptically from each animal. These were ground separately in a mortar with the aid of a pestle and the material suspended in a minimum of physiological saline. Each triturated organ was injected subcutaneously into the inguinal region of a normal guinea pig. These subinoculated animals were then followed by monthly tuberculin tests and autopsied as their reactions became positive, or after a four month period, whether they were positive or negative.

RESULTS

Tuberculosis by subinoculation was produced by each of the iliac nodes and by the spleens obtained from both the infected controls and the treated animals killed at the end of 3 days. All tissues obtained subsequently from the same organs of the animals killed at various intervals likewise produced tuberculosis when inoculated into normal guinea pigs.

The triturated bronchial nodes obtained from the treated pigs and the controls at the end of 3 and 5 days, when injected into normal guinea pigs, failed to produce tuberculosis. The bronchial nodes obtained from two infected controls, when subinoculated at the end of 10 days, produced progressive tuberculosis in normal guinea pigs, whereas the nodes obtained from the treated animals failed to do so. The tracheobronchial nodes from the two treated animals killed at 15 days, however, did produce tuberculosis on subinoculation. At 21 days, the tracheobronchial nodes from one of the treated animals produced tuberculosis on subinoculation, but those from the other failed to do so.

Pathologic Changes

Recordings of gross observations on all animals were made at autopsy. The spleen, liver, lungs, and the tracheobronchial and iliac nodes from each animal were then fixed in Zenker's solution and stained with hemotoxylin and eosin for microscopic study. The essential pathologic findings are presented in table 1, in which the gross and microscopic observations of the various organs are recorded according to the duration of the disease. As previously stated, two treated and two control animals were killed at each sacrifice period. The lesions in each of the animals within each group were, in most instances, comparable. When the described lesion appeared in only one of the animals, this fact is indicated by an asterisk.

In relation to the controls, it is evident that the treated animals exhibited little disease, that fewer organs were involved, and that, with one exception, the lesions were less extensive. The exception occurred in the iliac nodes of the animals sacrificed at 10 days; the extent of the disease was identical in each animal of the two groups and the lesions covered several microscopic fields.

It is important to emphasize the fact that lesions were observed in the spleen and lungs, although these lesions were only microscopic. The livers also might have revealed lesions had serial sections been made on this organ. A portal scar was observed in one of the treated animals killed at 27 days; this probably represented a healed tuberculous lesion. The iliac nodes of the animals killed at 27 days showed caseation.

The foci of lymphocytes seen in the lungs of the treated animals sacrificed

TABLE 1

Gross and Microscopic Pathological Findings in Streptomycin-treated and Nontreated Animals in Relation to Time after Infection

SACRIFICE PERIODS	TYPE OF PATHOLOGY	TREATED ANIMALS					CONTROL ANIMALS				
		Iliac node	Spleen	Lung	Liver	Tracheo-bronchial node	Iliac node	Spleen	Lung	Liver	Tracheo-bronchial node
3 days	Gross	Slight enlargement	0	0	0	0	Slight enlargement	0	0	0	0
	Microscopic	0	0	0	—	0	0	0	0	—	0
5 days	Gross	Slight enlargement	0	0	0	0	Slight enlargement	0	0	0	0
	Microscopic	0	0	Foci of lymphocytes*	—	0	0	0	0	—	0
10 days	Gross	Enlarged	Slight enlargement	0	0	Slight enlargement	Enlarged	Enlarged with tubercles	0	0	Enlarged
	Microscopic	Macrophages in sinuses	0	Foci of lymphocytes	—	0	Macrophages in sinuses	Macrophages	Macrophages	—	0
15 days	Gross	Enlarged	0	0	0	0	Tubercles	Tubercles	Tubercles	Tubercles	Tubercles
	Microscopic	Macrophages in sinuses	0	0	—	0	Macrophages, epithelioid tubercles and necrosis	Macrophages and epithelioid tubercles	Epithelioid tubercles	Epithelioid tubercles	Epithelioid tubercles
21 days	Gross	Enlarged	0	Translucent foci**	0	Slight enlargement	Tubercles	Tubercles	Tubercles	Tubercles	Tubercles
	Microscopic	Macrophages and necrosis	Macrophages	Foci of lymphocytes	0	0	Macrophages, epithelioid tubercles and caseation	Macrophages, epithelioid tubercles and caseation	Macrophages, tubercles and caseation	Epithelioid tubercles with caseation	Macrophages, epithelioid tubercles

27 days	Gross	Tubercles	0	0	0	0	Caseous foci	Tubercles	Tubercles	Tubercles	Tubercles
	Microscopic	Epithelioid tubercles with caseation	0	Epithelioid tubercles and foci of macrophages	Small scar**	0	Epithelioid and caseous tubercles	Necrosis, epithelioid tubercles and caseation	Macrophages, epithelioid cells and caseation	Epithelioid tubercles and caseation	Epithelioid tubercles and caseation
39 days	Gross	Slight enlargement	0	0	0	0	Caseous tubercles	Necrotic	Tubercles	Tubercles	Caseous tubercles
	Microscopic	Few macrophages and scar	0	0	0	0	Epithelioid and caseous tubercles	Macrophages, epithelioid tubercles and necrosis	Macrophages and caseation	Epithelioid and caseous tubercles	Epithelioid and caseous tubercles

* See text. ** Noted in only one of the animals.

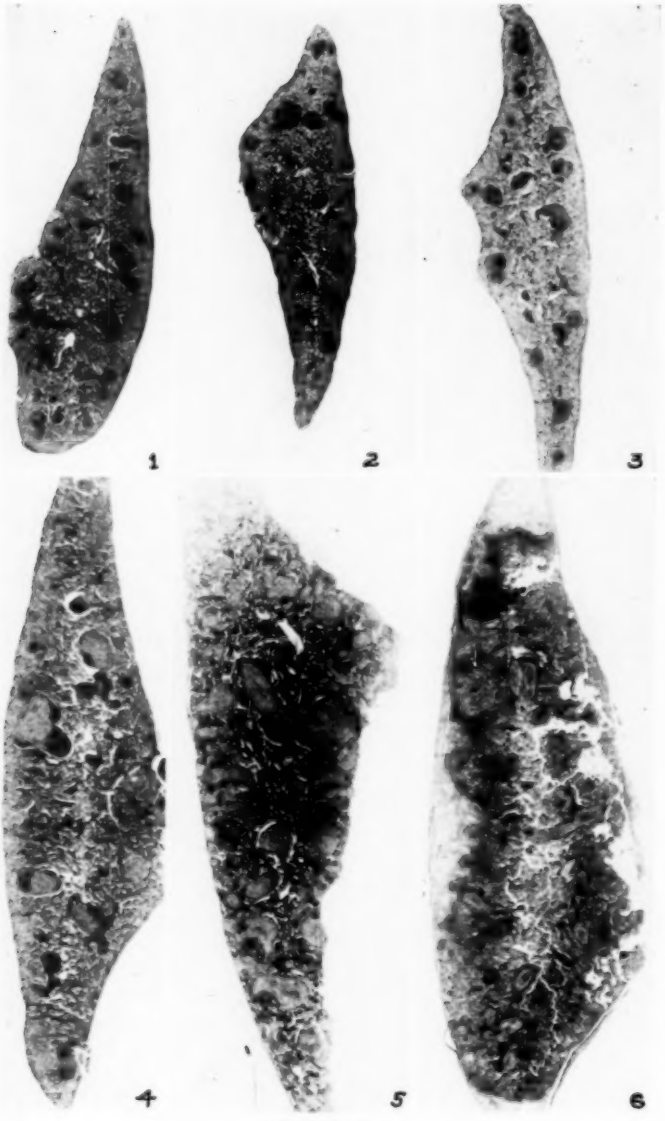

PLATE I.

Magnification of cross sections of spleens. ×10

FIG. 1. Treated animal 15 days after infection.

FIG. 2. Treated animal 21 days after infection.

FIG. 3. Treated animal 39 days after infection.

FIG. 4. Control animal 15 days after infection.

FIG. 5. Control animal 21 days after infection.

FIG. 6. Control animal 39 days after infection.

Note the increased size of the spleens of the control animals with progressing destruction of the malpighian bodies at 15 and 27 days, and the areas of necrosis at 39 days. Compare the relatively constant and normal size of the spleens of the treated animals. Microscopic evidence of tuberculosis was present in the spleen of the treated animals at 21 days (See Plate III, figure 2).

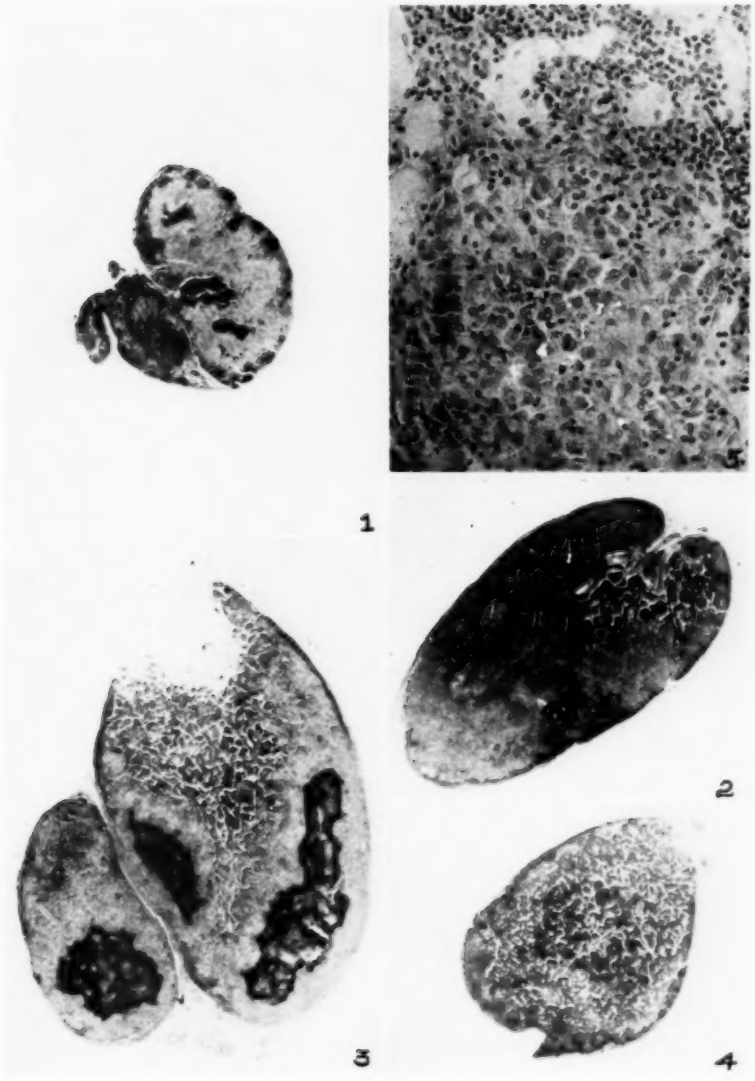

PLATE II.

Magnification of sections of iliac lymph nodes

FIG. 1. Treated animal 21 days after infection. ×10.

FIG. 2. Control animal 21 days after infection. ×10.

FIG. 3. Control animal 39 days after infection. ×10.

FIG. 4. Treated animal 39 days after infection. ×10.

Note the larger size of the iliac node in the control animals, also the lesions, with caseation, in the node from the animal treated 21 days, and the absence of a lesion at 39 days.

FIG. 5. Higher magnification of node shown in figure 1. Note infiltration with macophages and suggestion of formation of epithelioid cells. ×160.

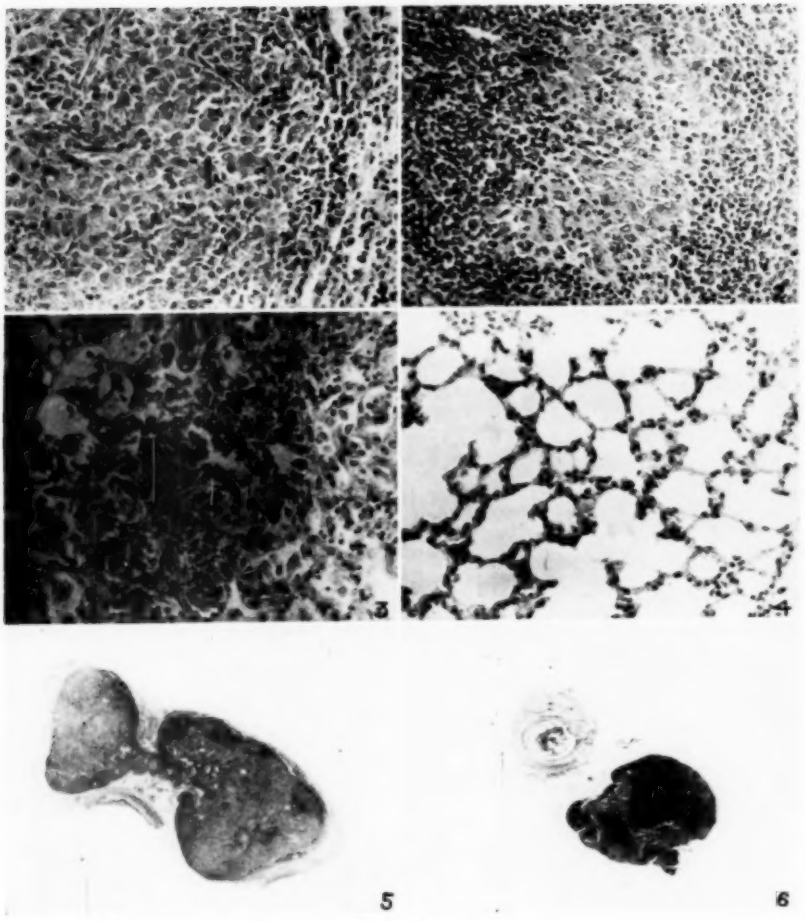

PLATE III

FIG. 1. Section of spleen from control animal at 21 days. ×160. Note destruction of malpighian body by macrophages and epithelioid cells. The margin of the malpighian body is at the right.

FIG. 2. Section of spleen from treated animal at 21 days. ×160. Note the infiltration within a malpighian body of macrophages, and epithelioid cells.

FIG. 3. Section of lung from control animal at 39 days. ×160. Note tuberculous pneumonia.

FIG. 4. Section of lung from treated animal at 39 days. ×160. Note absence of lesion.

FIG. 5. Section of tracheobronchial nodes from control animal at 39 days. ×10. Note enlargement and loss of structure due to the presence of epithelioid tubercles and caseation.

FIG. 6. Section of tracheobronchial node from treated animal at 39 days. ×10. Note absence of lesion. Node is of normal size.

on the fifth and tenth days were very conspicuous; they were compact, and many of them had germinal centers, evidence which indicated that they could be considered true lymphoid follicles. While such lymphoid foci are not normally present in the lung of the guinea pig, they were found rather frequently. The reason for their presence is not apparent. Little significance is attached to them, since in other experiments there has been no regular occurrence of such lymphoid foci in the lungs of treated animals. Aside from these lymphoid foci, the microscopic appearance of the lesions in the two groups was similar, and apparently streptomycin did not affect the cellular reaction to the bacilli (See figures).

DISCUSSION

The results of this experiment reveal that streptomycin therapy begun forty-eight hours prior to injection subcutaneously with virulent organisms did not prevent the distribution of tubercle bacilli in the body of the guinea pig. The fact that tubercle bacilli were demonstrated in the tracheobronchial lymph nodes of the control animals by subinoculation at 10 days, but not until 15 days in the treated animals, is not considered significant because this variation is within the range reported by Krause (1, 2). However, this finding may be contrasted with Krause's observation that in the immunized guinea pig the dissemination of bacilli from the site of inoculation is delayed. These observations indicate that the effect of treatment with streptomycin does not duplicate this phenomenon of host-acquired resistance inasmuch as streptomycin limits the multiplication of tubercle bacilli but does not result in the localization of the organisms at the site of inoculation.

The difference in the amount of tuberculosis observed in the two groups is striking and needs no further comment, for the dramatic effect of streptomycin on experimental tuberculosis in the guinea pig is well known. Nevertheless, the fact that tuberculous lesions developed in the treated animals deserves the closest study.

A review of the course of the infection in the treated animals shows that lesions were first seen in the iliac nodes at 10 days. Progression of this lesion was slow but definite up to 27 days, at which time caseation was present. At 39 days, the next sacrifice period, only a few macrophages and a small area of scar tissue were present. In the spleen, foci of macrophages were observed in the malpighian bodies at 21 days, but not before or after this period. At 27 days, small groups of macrophages and a few epithelioid tubercles were observed in several of the lymphoid foci in the lungs. At 39 days, both these and the lymphoid foci were absent, and the lungs appeared to be normal. It is apparent then that, despite streptomycin therapy, the tuberculous lesions progressed for a period of about 27 days, then regressed, and at 39 days the only lesions observed were a few macrophages and a scar in the iliac node.

The presence of caseation indicates that the animals had become hypersensitive. The animals killed at 27 and 39 days were skin tested with 5 per cent Old Tuberculin and both the control and the treated animals showed strong

positive reactions. Since it is known that hypersensitivity and acquired resistance appear at about the same time (9, 10), it is assumed that these animals had developed some resistance at this time. Thus, the cessation of progression and the appearance of a regressive tendency of the lesions in the treated animals coincided with the development of acquired resistance.

The fact that the treated animals became hypersensitive to tuberculin is also significant. It has been established that very small numbers of dead tubercle bacilli will not produce skin hypersensitivity when injected into guinea pigs subcutaneously. Apparently, the organisms multiplied in the animals despite streptomycin therapy.

The above considerations lead us to believe that streptomycin acts in conjunction with acquired resistance in the guinea pig, and that acquired resistance plays an important part in the dramatic results seen when an established tuberculosis in the experimental animal is treated with streptomycin.

Further experiments are in progress to study the early course of tuberculosis in guinea pigs immunized with living attenuated H37 Ra microorganisms, before treatment with streptomycin and infection with H37 Rv organisms.

CONCLUSION

1. The early dissemination of tubercle bacilli in the normal guinea pig is not affected by streptomycin therapy.

2. Although streptomycin limits the progression of tuberculous lesions in the guinea pig, lesions do progress despite adequate therapy, until acquired host-resistance develops, as shown by the development of skin hypersensitiveness.

CONCLUSIONES

La Estreptomicina en la Tuberculosis Experimental. III. Efecto sobre la Patogenia de la Tuberculosis Temprana en el Cobayo Infectado con Bacilos Tuberculosos H37 Rv Estreptomicinosensibles

1. La diseminación temprana de bacilos tuberculosos en el cobayo normal no es afectada por la estreptomicinoterapia.

2. Aunque la estreptomicina limita la agravación de las lesiones tuberculosas en el cobayo, las mismas continúan avanzando a pesar de una terapéutica adecuada hasta que se establece resistencia adquirida en el huésped, según revela la aparición de hispersensibilidad cutánea.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS[1,2]

IV. Effect on the Pathogenesis of Early Tuberculosis in Guinea Pigs Infected with Streptomycin-resistant H37 Rv Tubercle Bacilli

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INTRODUCTION

In a previous paper (1), observations on the early course of experimental tuberculosis in streptomycin-treated and nontreated guinea pigs were presented. The infecting microorganisms used in that experiment were the H37 Rv streptomycin-sensitive tubercle bacilli (sensitive to 0.4 γ per cc. of streptomycin) when tested in Tween-albumin medium. In the present experiment, microorganisms (H37 Rv) were used which had been made resistant *in vitro* to 1,000 γ of streptomycin per cc. in Tween-albumin medium. Except for the change in the infecting microorganisms used, the conditions of the previous experiments were repeated as nearly as possible.

MATERIALS AND METHODS

A stock culture of H37 Rv streptomycin-sensitive tubercle bacilli was made resistant to the drug by repeated subculture in gradually increased concentrations of streptomycin until it had developed a resistance to more than 1,000 γ of streptomycin per cc. (2). This strain was subcultured in the presence of 1,000 γ of streptomycin per cc. of medium for six months.

Preparation of suspension of bacilli: An evenly dispersed 14 day growth of the highly resistant tubercle bacilli in Tween-albumin medium was diluted with physiological saline until it gave a reading of 17 in the Klett Summerson colorimeter. This produced a suspension containing approximately 20,000,000 tubercle bacilli per cc.

Infection: Twenty tuberculin-negative male guinea pigs, each averaging 450 Gm. in weight were used. Each animal was injected subcutaneously in the midline anterior to the symphysis pubis with 0.2 cc. of the suspension, or approximately 4,000,000 tubercle bacilli.

Therapy: Ten of the animals were used as infection controls and the other 10 were treated with streptomycin. Each of the treated animals was given an initial dose of 4,000 units of the drug forty-eight hours before infection, and thereafter 18,000 γ were administered daily in four divided doses: three doses of 4,000 each at 7 a.m., 12 noon, and 5:30 p.m., and an evening dose of 6,000 at 10:30 p.m. Treatment was continuous through the experiment.

Sacrifice periods: Two treated and 2 control animals were sacrificed 6, 12, 18, 38, and 66 days after infection. Studies by tissue subinoculation were not made on these animals since it was assumed that, on the basis of the previous experiment (1), the rate of spread of the resistant organisms in the control animals would be identical (or in exact ratio) to the spread of the sensitive organisms in the nontreated animals. The spread of the disease in the treated animals was obvious and did not necessitate subinoculation.

RESULTS

The essential gross and microscopic observations are summarized in the accompanying table which shows that lesions developed in the various organs at the

[1] From the Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

[2] This study was aided by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

same intervals after infection and progressed at similar rates in the treated and in the control animals. In many instances, there appeared to be fewer Langhans' cells associated with the lesions in the treated animals than in the controls, but no gross and no other histological distinctions could be made.

PLATE I

FIG. 1. Low power magnification of spleen from animal treated 66 days. Compare with figure 2. Note similar degree of enlargement. Tuberculous lesions are present in the malpighian bodies. ×10. (See Plate II, figure 1)

FIG. 2. Lower power magnification of spleen from control animal at 66 days. ×10.

COMMENT

The results of this experiment indicate clearly that guinea pigs infected with H37 Rv tubercle bacilli that were made highly resistant to streptomycin (1,000 γ or more) by *in vitro* adaptation do not respond to streptomycin therapy.

Other experiments to be reported from this laboratory by Steenken and Wolinsky (3) will show that guinea pigs infected with tubercle bacilli freshly isolated from patients under streptomycin treatment, and which have become

resistant to much lower concentrations than 1,000 γ of the drug per cc. of Tween-albumin medium, do not respond to streptomycin therapy. The same authors have also noted that a rough approximation of the relative number of drug-

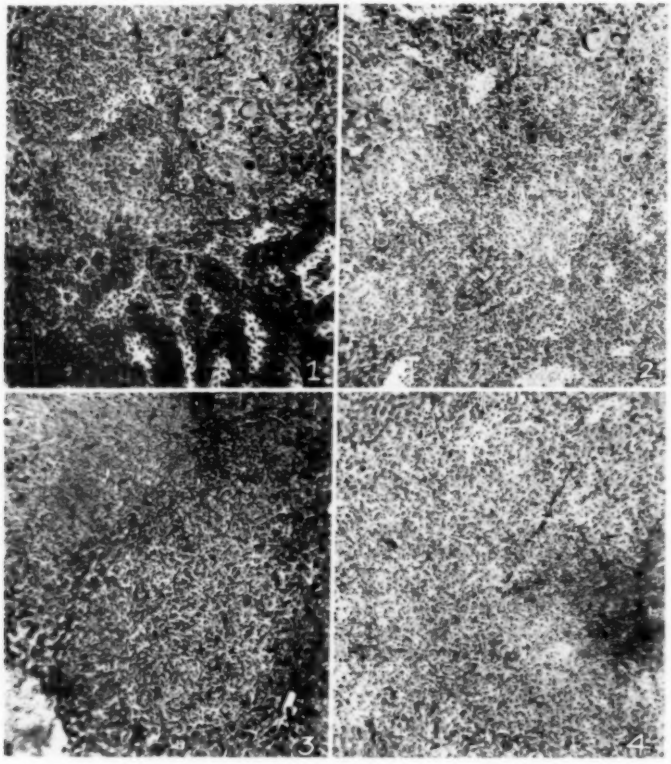

PLATE II

FIG. 1. Spleen from animal treated 66 days. Note unencapsulated epithelioid tubercles. One multinucleated giant cell is present in this field. ×120.

FIG. 2. Spleen from control animal 66 days. Note similarity to figure 3. Several multinucleated giant cells are present. ×120.

FIG. 3. Liver from animal treated 66 days. Note the presence of unencapsulated epithelioid tubercles. Necrosis is present in the center of the left upper quarter of the field. ×120.

FIG. 4. Liver from control animal at 66 days. Note similarity to figure 3. Necrosis is more obvious in this field. ×120.

resistant tubercle bacilli in a culture can be made by observing the length of the lag period before growth appears in a given concentration of the drug. It is possible that when resistance develops in a patient it is gradual and, therefore,

TABLE 1

Gross and Microscopic Pathological Findings in Streptomycin-treated and Nontreated Animals in Relation to Time after Infection

SACRIFICE PERIODS	TYPE OF PATHOLOGY	TREATED ANIMALS					CONTROL ANIMALS				
		Iliac node	Spleen	Lungs	Liver	Tracheobronchial node	Iliac node	Spleen	Lungs	Liver	Tracheobronchial node
6 days	Gross	Slightly enlarged	Slight* enlargement	0	0	0	Slightly enlarged	Slight* enlargement	0	0	0
	Microscopic	Macros in sinuses	0	0	0	0	Macros in sinuses	0	0	0	0
12 days	Gross	Enlarged with tubercles	Slight enlargement	0	0	Slight enlargement	Enlargement with tubercles	Slight enlargement	0	0	Slight enlargement
	Microscopic	Tubercles with necrosis	0	0	0	Macros* with sinuses	Tubercles with necrosis	One tubercle	One* tubercle	0 0	Macros in sinuses
18 days	Gross	Enlarged with caseous foci	Enlarged	Yellow flecks	Scattered tubercles*	Slight enlargement	Enlargement with caseous foci	Enlarged with tubercles*	Yellow flecks*	Scattered tubercles	Slight enlargement
	Microscopic	Epithelioid tubercle with caseation	Epithelioid tubercles	Epithelioid* tubercles + necrosis	Epithelioid tubercles	Epithelioid tubercles	Epithelioid tubercles + caseation	Epithelioid* tubercles + necrosis	Epithelioid tubercles	Epithelioid* tubercles	Epithelioid tubercles
38 days	Gross	Enlarged 4×	Enlarged 3×	Slight enlargement with gray flecks	Many tubercles	Enlarged 3×	Enlarged 4×	Enlarged 3×	Slight enlargement with gray flecks	Many tubercles	Enlarged 5×
	Microscopic	Epithelioid + caseous tubercles scarring	Epithelioid caseous tubercles	Epithelioid tubercles with caseation	Epithelioid + caseous tubercles	Epithelioid + caseous tubercles scarring	Epithelioid + caseous tubercles	Epithelioid + caseous tubercles	Epithelioid tubercles with caseation	Epithelioid + caseous tubercles	Epithelioid + caseous tubercles

* Noted in only one of the animals.

he may still respond to therapy for a certain period of time until his resistant organisms become predominant, and the patient no longer responds to the drug.

CONCLUSIONS

1. The early course of the disease in guinea pigs infected with H37 Rv tubercle bacilli resistant to 1,000 γ of streptomycin per cc. was not appreciably altered by streptomycin therapy.

2. Pathological lesions of tuberculosis under the conditions of this experiment were similar in extent in the treated and the control animals. The histological appearance of the lesions was similar in the two groups except that fewer Langhans' cells were seen in the treated animals.

CONCLUSIONES

La Estreptomicina en la Tuberculosis Experimental. IV. Efecto sobre la Patogenia de la Tuberculosis Temprana en los Cobayos Infectados con Bacilos Tuberculosos H37 Rv Estreptomicinorresistentes

1. La evolución temprana de la tuberculosis en cobayos infectados con bacilos tuberculosos H37 Rv resistentes a 1,000 γ de estreptomicina por cc. no fué alterada apreciablemente por la estreptomicinoterapia.

2. En las condiciones de este experimento, la patología de la tuberculosis es semejante en extensión en los animales tratados y los testigos. El aspecto histológico de las lesiones fué también semejante en los dos grupos, salvo por observarse menos células de Langhans en los animales tratados.

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TRANSITORY INFILTRATES IN THE LUNGS WITH EOSINOPHILIA (LOEFFLER'S SYNDROME) [1]

A Review With the Report of a Case

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REVIEW OF THE LITERATURE

The syndrome of pulmonary infiltration of brief duration associated with eosinophilia was described by W. Loeffler of Zürich in 1932 (1). By 1936 (2) he had accumulated 51 cases. Although most of this material came from chest clinics, in no instance was there any evidence of active pulmonary tuberculosis.

This group was of special interest because of the difficulties in differential diagnosis. The shadows observed in the lung fields were of many types, varied in distribution and were remarkable for their fleeting character. In some patients the process was migratory. Another distinguishing characteristic was the presence of an eosinophilia. In more than half of these individuals, the eosinophils ranged between 10 and 30 per cent. The highest percentage of eosinophils observed was 66. There was no strict parallel between the size of the infiltrate and the accompanying eosinophilia. The maximum number of eosinophils was found at the time when the pulmonary shadows had begun to resolve. Very often, the eosinophilia persisted for a long time after the clearing of the pulmonary process in the roentgenogram. The symptomatology also bore no constant relation to the extent of the physical and roentgenological findings.

Fourteen of Loeffler's 51 cases were entirely symptom-free. In these patients the pulmonary shadows were discovered during the course of routine fluoroscopy or roentgenographic surveys. The majority of the patients complained chiefly of fatigue and of respiratory symptoms of varying severity. The condition was encountered most frequently between July and August. Fully two-thirds of the patients were males. Two instances were found in members of the same family. All the cases followed a benign course regardless of the therapy employed. The individuals observed in Loeffler's series were of different age groups; one-third were small children. Thirteen had negative skin reactions to tuberculin, while the remaining 37 were tuberculin-positive.

Since Loeffler's observations, the literature on the subject has grown considerably. Reports have come from all parts of the world. Virtually all authors now agree that the condition is an allergic reaction occurring in the lungs of a sensitized individual. Most of the patients are found to have an allergic background and to have had other manifestations of allergy. The number and variety of conditions in which Loeffler's syndrome has appeared is constantly increasing and may be limitless. Cases have been reported in the course of, or in association with, various bacterial infections, parasitic infestations, asthma, pollen sensitivity, and other allergic states, erythema nodosum, periarteritis no-

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dosa, drug therapy, and exposure to physical agents. The syndrome has appeared in groups (21), in "epidemics" (22) and sporadically. The latter occurrence is more frequent.

In some instances the process in the lungs and the eosinophilia have recurred in the same individual. In others they have followed a more prolonged course of from several weeks to several months and have been associated with severe manifestations in other organs. Harkavy (3) reported a series of 16 cases of bronchial asthma with diffuse vascular involvement, almost all of which showed Loeffler's Syndrome on one or more occasions over a period of several years.

Because of the apparently benign course in most persons affected, very few studies of the tissues have been made in the living patient. The sputum (3, 14), pleural fluid (3, 14), peritoneal fluid (3), lung puncture (14), and muscle biopsy (3) material have shown a preponderance of eosinophils when examined.

Von Meyenburg (4) described the postmortem findings in 4 cases of accidental death, one of which followed traumatic tetanus. These are believed to show Loeffler's Syndrome. In 3 there were areas of focal pneumonia; in 2 there were bronchopneumonias in which the exudate was largely eosinophilic; and one showed evidence of beginning organization of the exudate in a few places. Two showed eosinophilic bronchitis and bronchiolitis. Perivascular and interstitial lesions were also described. In one instance a necrotic focus was found in a pneumonic area. Some areas of thrombophlebitis were found in the septal veins, none of which was completely obstructed. Eosinophilic infiltration was found in the other organs, particularly in the bone marrow and in the liver. Charcot-Leyden crystals were found especially after the tissues had lain in the refrigerator.

Von Meyenburg felt that the anatomic basis of Loeffler's Syndrome had been demonstrated. He did not feel that the fleeting nature of the lesions had been proved, at least in one of the cases, because of the nature of the involvement of the interstitial tissues and blood vessels. This would correspond with the cases of longer duration described by several authors (5, 6, 7, 8, 9, 10, 11, 12). He concluded that the lung lesions of Loeffler's disease "are really exudative foci, eosinophilic pneumonias."

He also described a nonspecific eosinophilic epididymitis in an operative specimen removed from a patient who had a transient lower lobe shadow associated with eosinophilia. From this observation, as well as from the findings in the other patients, he concluded that eosinophilic infiltrates occur simultaneously in other organs. Of the 6 deaths in Harkavy's (3) series, 4 came to postmortem examination. The lungs showed congestion, edema, and infiltration of the interalveolar septa with eosinophils, neutrophils, and lymphocytes as well as edema. There were also noted atelectasis, emphysema, and infarction, depending on the preceding course and complications. The bronchi exhibited the changes commonly seen in asthma. Most interesting were the lesions in the blood vessels varying from simple thickening of small vessels involving the intima to an acute necrotizing arteritis with periarterial eosinophilic infiltration and endarteritis obliterans. In the pleura there were sclerosis of small vessels

and inflammatory exudate with eosinophilia. The other organs showed similar vascular lesions. In 2 of these autopsies a pathological diagnosis of periarteritis nodosa was made.

Bagenstoss, Bayley, and Lindberg (13) report on the postmortem pulmonary findings in a case of Loeffler's Syndrome. The lungs showed scattered tubercle-like granulomata. In some areas there was organization of the alveolar exudate. A more recent acute inflammatory process was found in the lower lobes with a predominance of eosinophils in the exudate. The bronchioles contained mucus and desquamated epithelial cells. Their walls were infiltrated with eosinophils and plasma cells. Perivascular inflammatory lesions with thickening and occasional necrosis of the vessels walls were also present.

Von Meyenburg (4), Nagel (14), and Herbut and Kinsey (23) cited experimental work (15, 16, 17) in which the various clinical and pathological findings observed in individuals with eosinophilic lung infiltrates have been reproduced. Hansen-Pruss and Goodman (18), Bagenstoss, Bayley and Lindberg (13) and Harkavy (3) mention the role of the vascular system in producing the findings in their patients. They refer to the work of other authors wherein similar vascular lesions are found to be on an allergic basis. Alpher (19) regards the occurrence of eosinophilic infiltrates in other organs as postulating a hematogenous pathway for the "intrinsic type" of case and he raises the possibility that Loeffler's Syndrome may be due to viral infection in an essentially allergic person. He also regards the interstitial tissue as the shock organ whereas Hansen-Pruss and Goodman (18) offer the view that in the course of repeated respiratory infections there is possible sensitization of the bronchial tree by bacteria with allergic response in the form of a pneumonic type of reaction to reinfection with the sensitizing antigen or with some other antigen.

The importance of the syndrome lies in the problem of differential diagnosis which it presents. Some cases have been mistaken for tuberculosis, as with the patient in the present report, some for lung abscess or infarcts, and others for pneumonia of various kinds.

The types of shadows seen on the chest roentgenograms, according to Loeffler (2) are:

1. Large, more or less irregular shadows, unilateral or bilateral.
2. Small round foci.
3. Multicentric unilateral or bilateral infiltration.
4. Lobar shadows.
5. Infiltrates simulating "secondary tuberculous infection."
6. Cases with pleural involvement and a very small fleeting effusion.

In addition to the varied shadows noted by others, Hennell and Sussman (15) describe:

narrow, plate-like homogenous densities. . . . .extending obliquely caudad and laterally. Often they are symmetrical in the two lungs. They also resolve completely. Whether they represent localized exudations in the lung or pleura is impossible to state, but they seem to be unique to this disease. There is no predilection for upper or lower lobes, but a fair degree of symmetry on the two sides is the rule.

The physical signs are variable depending upon the extent of involvement. The following case is reported as an instance of Loeffler's Syndrome.

CASE REPORT

S. P., a 44 year old white housewife and factory worker, was a known asthmatic for about six years. Following an episode of bronchopneumonia in 1939, the asthmatic attacks first appeared and increased in severity. There was no familial history of allergy. The patient had been studied in the Allergy Clinic and was found to be slightly sensitive to dust, cat dander, dog dander, goat hair, flaxseed, cotton seed, tobacco, and white potato. The last asthmatic attack followed a cold during August, 1945. For three weeks prior to the first visit to the Medical Clinic on September 13, 1945, the patient had noted fatigue, dyspnea on effort, irritability, nervousness, loss of appetite and a 10 pound loss of weight.

A chest roentgenogram taken September 13, 1945 (figure 1) revealed heavy infiltration throughout the upper portions of both lung fields, more prominent on the left side. There was some patchy infiltration in the lateral portion of the right lung opposite the hilum and near the diaphragm. The cardiac shadow showed slight generalized enlargement.

A blood count performed on September 13, 1945 showed: erythrocytes 4,400,000, hemoglobin 13 Gm. per 100 cc., leukocytes 12,300 per cu. mm., neutrophils 62 per cent, lymphocytes 24 per cent, eosinophils 14 per cent. The urine was normal and the blood pressure in mm. of mercury was 110 systolic and 70 diastolic. The patient was referred to the Pulmonary Clinic where examination on September 24, 1945 revealed dullness at both apices. No rales were heard. Hospitalization for tuberculosis was advised. She was admitted to another hospital on September 26, 1945 with the diagnosis of bilateral pulmonary tuberculosis, far advanced. On admission the blood pressure was 170 systolic and 100 diastolic. Otherwise there was no change in the physical findings.

A roentgenogram of the chest obtained on September 28, 1945 (figure 2) showed dense infiltration diffusely distributed throughout the left lung. The upper portions of the right lung field revealed similar, though less extensive, infiltrates. A subsequent roentgenogram taken on December 21, 1945 (figure 3) showed that the pulmonary infiltrates had resorbed completely. There was marked enlargement of the heart when compared with the cardiac silhouette in the previous film.

The treatment consisted of bed rest with symptomatic therapy. Examinations of five sputum concentrates were negative for acid-fast bacilli. The sedimentation rate was 32 mm. per hour. During her stay in the hospital the patient gained ten pounds in weight. The final diagnosis on discharge was nontuberculous pulmonary disease, probably pneumonia.

FIG. 1. Chest roentgenogram taken on September 13, 1945 shows an exudative infiltrate involving the upper portions of both lungs, but more dense and extensive on the left. The lateral portions of the right first to fourth anterior interspaces and of the base are also involved.

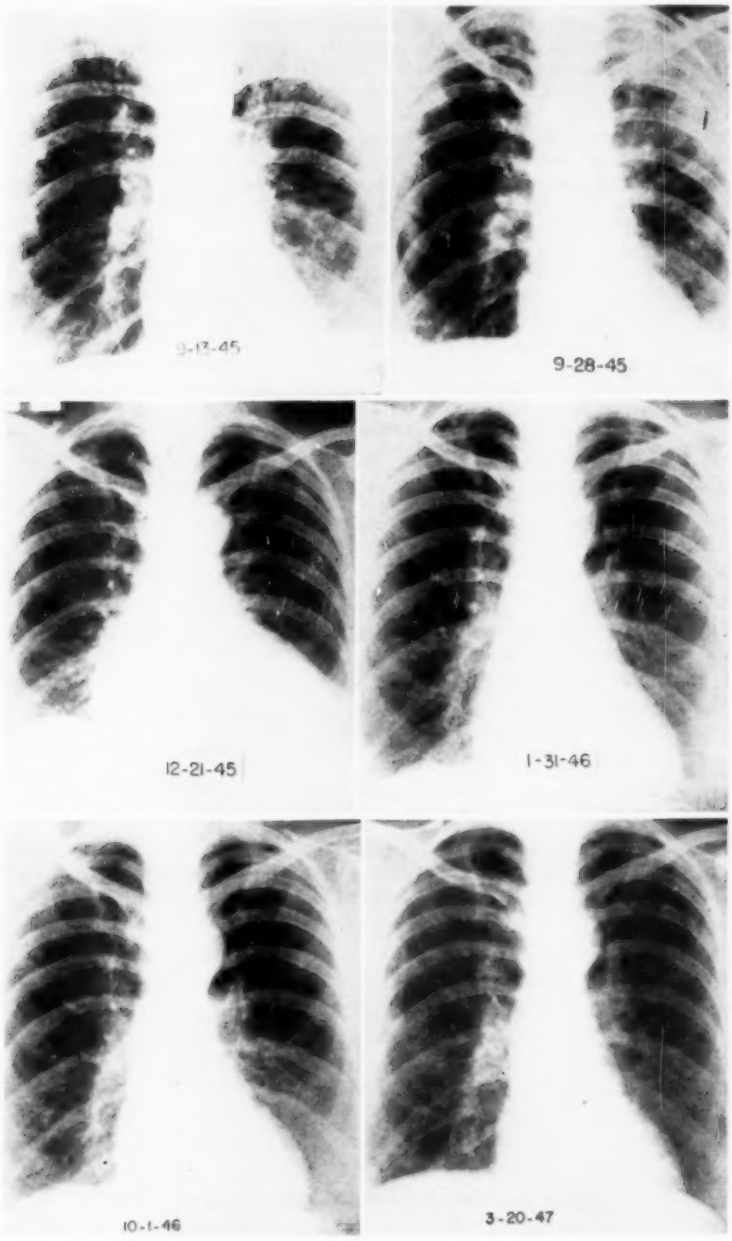
FIG. 2. Chest roentgenogram taken on September 28, 1945 shows some clearing in the right upper lung field. There has been some increase in the shadows previously noted at the periphery and base of the right lung. The left shows shadows of varying size and density throughout.

FIG. 3. Chest roentgenogram taken on December 21, 1945. The lung fields are clear except for some accentuation of the markings and fine nodular mottling in the lower portions. The heart is considerably enlarged.

FIG. 4. Chest roentgenogram taken on January 31, 1946. The lung fields are clearer; the markings somewhat accentuated. The heart is smaller.

FIG. 5. Chest roentgenogram taken on October 1, 1946. The lung fields are clear. The heart is smaller.

FIG. 6. Chest roentgenogram taken on March 20, 1947. Lung markings are accentuated. The heart is unchanged.



FIGS. 1-6

The patient returned to the Pulmonary Clinic on February 4, 1946 with complaints of nervousness and irritability. Physical examination revealed clear lungs. The blood pressure in mm. of mercury was 144 systolic and 92 diastolic.

A roentgenogram taken on January 31, 1946 (figure 4) again showed complete clearing in both lung fields.

The Mantoux test was positive to 0.01 mg. of Old Tuberculin. The stool contained no ova or parasites. A blood count on March 22, 1946 showed erythrocytes 4,600,000, hemoglobin 14.2 Gm. per 100 cc., leukocytes 11,500 per cu. mm. with 66 per cent neutrophils, 24 per cent lymphocytes, 7 per cent eosinophils, and 3 per cent basophils.

A diagnosis of Loeffler's Syndrome was made.

The blood pressure ranged from 160 systolic and 100 diastolic on January 19, 1946 to 142 systolic and 88 diastolic on March 25, 1946. An electrocardiogram taken on February 25, 1946 showed sinus tachycardia, left axis deviation, low diphasic T waves in leads I and II, and a small R wave in lead III.

The patient remained well until April 1946, when she was hospitalized because of cough, dyspnea and wheezing of two weeks' duration. The patient was believed to have a respiratory infection and was given penicillin intramuscularly. Epinephrin, aminophyllin and "benadryl" were used to control the wheezing which disappeared after a few days. She left the hospital feeling well. The blood pressure on admission had been recorded as 110 systolic and 80 diastolic but fluctuated between 142 and 110 systolic and 90 and 60 diastolic. The leukocyte count was 13,800 per cu. mm. with 78 per cent polymorphonuclears, and 22 per cent lymphocytes. Two specimens of sputum were negative for tubercle bacilli, and examination of the stool showed no ova or parasites. No roentgenogram was obtained on this admission.

Subsequently the patient had several less severe asthmatic attacks and was treated in the Allergy Clinic with aminophyllin and injections of vaccine and bacterial extract. On April 1, 1947 her total leukocyte count was 7,000 per cu. mm. with 56 per cent neutrophils, 28 per cent lymphocytes and 16 per cent eosinophils. The sputum was negative for tubercle bacilli and contained numerous eosinophils.

On October 1, 1946 (figure 5) a roentgenogram showed somewhat less prominent lung markings and some diminution in the heart size. The latter was slightly smaller than in the earliest film and the apex was more clearly defined. The most recent film take March 20, 1947 (figure 6) showed the markings somewhat more accentuated than in the two preceding films, but no increase in the heart size.

DISCUSSION

The illness of this patient, presented as showing Loeffler's Syndrome, seems to resemble those instances of longer duration and greater complexity with involvement of extrapulmonary organs which were described since Loeffler's original observations.

The changes in heart size and the elevated blood pressure in this patient suggest the possibility of widespread eosinophilic infiltration in the heart and other organs. Unfortunately, no electrocardiograms were taken during the period of greatest cardiac enlargement. No evidence of renal damage was found.

Some of Harkavy's (3) patients showed electrocardiographic changes, pericarditis, and signs of cardiac enlargement or failure. In the nonfatal cases the changes were reversible, but recurred with subsequent asthmatic attacks. All of his 6 fatal cases showed clinical or pathological signs of adhesive pericarditis. Three had constrictive pericarditis and 4 had polyserositis. One of Karan and Singer's (11) cases showed temporary cardiac enlargement, chiefly of the right ventricle. This was attributed to right ventricular strain and regressed with the

resorption of the pulmonary shadows. It will be interesting to follow this patient's course in the light of Harkavy's findings.

Experience with this patient serves to illustrate the differential diagnostic problem. In this instance pulmonary tuberculosis was suspected because of the symptoms and roentgen picture. The patient actually spent three months under observation for pulmonary tuberculosis.

Because the symptomatology may simulate both acute and chronic pulmonary diseases and since the roentgenographic findings are extremely varied, it is important that the patient be studied from the clinical as well as from the laboratory standpoints. Loeffler's Syndrome should be suspected if the blood count repeated at intervals of several days to a week shows eosinophilia. A careful history may disclose repeated respiratory infections superimposed on an allergic background such as asthmatic attacks, hay fever, migraine, et cetera.

Roentgenograms taken at intervals of one week will usually show rapid clearing or migration of the pulmonary shadows. The presence of the oblique shadows described by Hennell and Sussman (20) may be helpful. The sputum should be examined for tubercle bacilli. The absence of acid-fast organisms, especially when large lesions exhibiting lobar distribution and rarified areas suggesting cavitation are present, would tend to exclude a diagnosis of pulmonary tuberculosis. Pneumococcus pneumonia can be excluded by the failure to find pneumococci of the fixed types in the sputum. The use of the cold agglutination test may be valuable in ruling out the atypical pneumonias. The absence of foul or purulent sputum and the rapid resolution help to separate these cases from lung abscess and suppurative pneumonia. Observation, bronchoscopy, and serial roentgenograms will differentiate Loeffler's Syndrome from carcinoma of the lung. Pulmonary infarct can be distinguished by the course and the absence of conditions with which it is usually associated.

Because of the frequent association of this syndrome with chronic infections, especially by protozoa, stool examinations, cutaneous tests, and serological procedures may be of great value in detecting unsuspected infections whose causative organisms may act as sensitizing and provocative antigens. A thorough allergic study with various antigens may be advisable. As this condition may be but one manifestation of a serious underlying disease such as periarteritis nodosa, especially in the more protracted or recurrent cases, appropriate steps should be taken to exclude this possibility.

SUMMARY

A case of Loeffler's Syndrome in a 44 year old woman is presented. Transitory cardiac enlargement and mild hypertension were also observed.

SUMARIO

Infiltraciones Transitorias en los Pulmones con Eosinofilia (Síndrome de Loeffler)

Este caso de síndrome de Loeffler en una mujer de 44 años coexistió con hipertrofia cardíaca pasajera y leve hipertensión. El síndrome de Loeffler pasa por ser un fenómeno alérgico exudativo en los pulmones.

Acknowledgment

The authors wish to acknowledge the courtesy of Dr. F. J. McCarthy in allowing them to use the records of this case at St. Joseph's Hospital, Bronx, New York, N. Y.

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TUBERCULOUS ESOPHAGO-CUTANEOUS FISTULAE TREATED WITH STREPTOMYCIN AND GASTROSTOMY[1]

Report of a Case

JOHN F. LAWSON[2]

(Received for publication June 28, 1948)

This case is presented primarily as an unusual form of tuberculosis and, secondly, because one phase of the disease responded to streptomycin.

CASE REPORT

History: A 28 year old, white, single female was admitted to North Carolina Sanatorium on October 7, 1947 with the following history. She enjoyed good health and normal development until 1924, when at the age of five she was exposed to a known case of tuberculosis. Shortly after this she is said to have developed measles and an upper respiratory infection, followed several weeks later by pain in the thoracic spine. A diagnosis of tuberculosis of the spine was made and a body cast was applied and worn for one year. In spite of this, she had a marked kyphosis over the lower cervical and upper thoracic vertebrae, which was painless and which allowed normal physical activity for the next twenty years.

In June, 1944 she noted a hard swelling the size of a hen's egg on the left side of the neck associated with generalized malaise and fever. Tuberculous abscess of a cervical lymph node was diagnosed and the swelling was later incised and drained with an indwelling tube. This area never healed, and eleven months later while drinking a beverage the patient discovered that the latter had seeped through the sinus and had wet the exposed surface of the neck. Pain reappeared in the spine and shortly thereafter, in 1945, a mass was noted on the right side of the neck. This, in due time, followed a course similar to that on the left. Both sinuses have continued to drain purulent material intermittently since 1945. Body cast was applied at that time and the patient continued to wear this. However, the pain in her spine persisted and the kyphosis became more marked.

Physical examination: Physical examination at the time of admission revealed a small, poorly developed and poorly nourished, white female who appeared chronically ill. Her temperature was 99° F., pulse 120 per minute and the respirations were 18 per minute. The blood pressure in mm. of mercury was 144 systolic and 100 diastolic. There was generalized wasting of the subcutaneous tissues. Examination of the head revealed nothing abnormal. The neck was thrust forward as a result of the spinal deformity. Bilateral, nontender, anterior cervical lymph nodes were felt. At the base of the neck on each side just anterior to the trapezius muscle were scarred areas the size of a half-dollar with small fistulous openings from which purulent material could be expressed. Fluids taken by mouth appeared promptly at these openings. There was marked kyphosis involving the lower cervical and upper thoracic vertebrae with a nontender gibbus involving the third and fourth thoracic vertebrae, and accompanying thoracic deformity of marked degree. The heart and lungs were normal on percussion and auscultation.

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Neurological examination was normal. The remainder of the physical examination was noncontributory.

Laboratory examination: Studies of the blood revealed no abnormalities except for 12,750 leukocytes per cu. mm. with 85 per cent neutrophils, 14 per cent small lymphocytes,

FIG. 1 FIG. 2

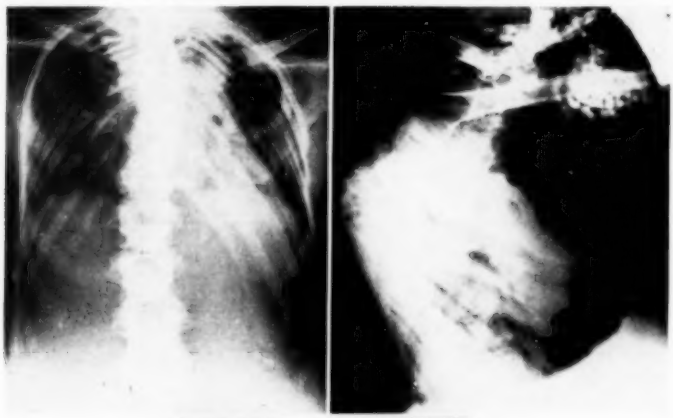

FIG. 3

FIG. 1. Chest roentgenogram demonstrating marked destruction of thoracic vertebrae.

FIG. 2. Lateral roentgenogram showing spinal deformity.

FIG. 3. Lipiodol was injected into both sinuses and could be traced by fluoroscopy into the esophagus and stomach. The saccular area in the region of the esophagus is not demonstrated in this roentgenogram.

and 1 per cent eosinophils. A serologic test for syphilis (Kline) was negative and the urinalysis was normal.

Roentgenograms of the chest showed no evidence of active pulmonary tuberculosis. There was definite widening of the superior mediastinum, however, particularly on the left. Roentgenograms of the spine revealed marked destruction of the dorsal vertebras as shown in figures 1 and 2. Lipiodol was injected into each sinus and this could be

traced by fluoroscopy into a saccular area that was continuous with the esophagus and stomach. This is shown in part by figure 3. The saccular area retained the opaque material only transiently. Sputum, examined repeatedly by concentration and culture, was negative for tubercle bacilli. Cultures from the draining fistulae revealed tubercle bacilli.

FIG. 4

FIG. 5

FIG. 4. Photograph representing topographical deformity of spine. Dressing on abdomen covers site of gastrostomy incision. Supraclavicular scar is visible but is shown in higher magnification in figure 5.

FIG. 5. Enlargement to show healed scar in supraclavicular region.

Course in hospital: A diagnosis was made of tuberculous spondylitis complicated by formation of mediastinal abscess, bilateral esophago-cutaneous fistulae, and bilateral tuberculous cervical lymphadenitis. Because of the results reported (1, 2) from the use of streptomycin in the treatment of draining tuberculous sinuses, this drug was used in this case. Esophagoscopy was attempted as a preliminary to chemotherapy, but was unsuccessful because of the spinal deformity. Intramuscular streptomycin, 1 Gm. a day in 3 doses, was begun on November 27, 1947.

On November 28, 1947 gastrostomy was performed in order to put the esophagus at rest during streptomycin therapy. The patient was fed via the gastrostomy and received nothing by mouth for seventy-two days. After one month of treatment the fistula on the left side closed, followed on the seventh week by closure of the fistula on the right. On February 6, 1948 the patient was given a soft, bland diet by mouth and on February 19 the fistula on the left side reopened. Streptomycin was discontinued on February 20 after the patient had received 86 Gm. in eighty-six days, the esophagus remaining free from food for seventy-two days during this period. The fistula on the left drained for three weeks and closed spontaneously and neither fistula has drained for the past three

FIG. 6. Barium swallow, three months after streptomycin was discontinued, demonstrating the distorted esophagus. No fistulous tracts are seen.

months.[3] After two previously unsuccessful attempts, the gastrostomy was closed on May 11, 1948.

At present the patient is taking a regular diet, eating well, and gaining weight. There are no palpable cervical lymph nodes. Figure 4 presents a photograph taken May 8, 1948 showing the deformity. Figure 5 illustrates the healed site of the previous fistulous opening on the left, ten weeks after streptomycin therapy was discontinued. The right side is not shown, but is identical with the left. Figure 6 presents the results of a barium swallow three months after streptomycin therapy and demonstrates the distorted esophagus which is deviated to

[3] Since this report was accepted for publication, the writer has been informed that one of the fistulae has reopened and continued to drain. No further streptomycin has been given.

the left in its upper portion. No fistulous tracts are seen. However, there is no knowledge of the condition of the presumed underlying mediastinal abscess.

The possibility that one or both fistulae were connected with the distal pharynx rather than the esophagus cannot be excluded with absolute certainty. The esophageal site is much more likely, however, because all of the pharynx, except the region of the junction between inferior constrictor muscle and esophagus, was observed under direct vision during the attempt at esophagoscopy.

SUMMARY

A case of tuberculous esophago-cutaneous fistulae treated with streptomycin is presented. Eighty-six grams of streptomycin were given over a period of eighty-six days. A gastrostomy was performed and for seventy-two days during the period of chemotherapy the patient was fed exclusively by tube. Both fistulae have remained closed for more than three months.[3]

SUMARIO

Fístulas Esófago-Cutáneas Tuberculosas Tratadas con la Estreptomicina y la Gastrostomía

El caso descrito es de fístulas esófagocutáneas tuberculosas tratadas con la estreptomicina, administrándose 86 Gm. de la droga durante un período de ochenta y seis días. Ejecutóse una gastrostomía y durante setenta y dos días de dicho período de quimioterapia el enfermo fué alimentado exclusivamente con sonda. Ambas fístulas han permanecido cerradas por más de tres meses.

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SKIN TUBERCULIN REACTION FOR THE ASSAY OF TUBERCULIN IN GUINEA PIGS[1]

GRAHAM CHEN AND R. W. SARBER

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INTRODUCTION

Since the initial discovery by Koch that tuberculin could be a useful aid in the diagnosis of tuberculosis, its use has grown until it now occupies a position of universal acceptance. Many of the problems that have arisen in the use of tuberculin have resulted from a lack of knowledge of its chemical and immunological characteristics. Attempts to correlate various separately conducted studies on tuberculin skin sensitivity have not always been entirely successful. This is easily understood when consideration is taken of the many and varied methods and steps in the preparation of tuberculins. The use of various nonsynthetic and synthetic media, concentration of filtrate to standard volume without regard to its activity, and various methods of partial purification, all contribute to the confused picture found in correlation studies.

The development by Seibert (1) of a highly purified tuberculin, Purified Protein Derivative (PPD), has greatly reduced the nonspecificity of tuberculin reactions and furnished an excellent material to use as a tool for the comparison of various tuberculin preparations. Attempts at standardization of tuberculins, however, have shown both the unreliability of present methods and a great variation among tuberculins from various sources. Savage (2), Sweany (3), Seideman (4), and others have compared tuberculins from various sources and found considerable variation among products. Early attempts were made by several to establish a quantitative biolcgical test. The determination of a minimal lethal dose of tuberculin injected subcutaneously into a tuberculous guinea pig was one of the earliest methods (5). Long (6) employed a method which determined the minimal amount of tuberculin which when injected into the testis of a tuberculous guinea pig would cause complete inhibition of spermatogenesis. Both of these methods proved impractical because results varied too greatly with the degree of tuberculin sensitivity. Bunney and Gottschall (7) and Clark and Follin (8) have presented semi-quantitative methods based upon comparative skin reactions in guinea pigs.

In view of the importance of the dosage of tuberculin in diagnostic, therapeutic, and prophylactic procedures, a standard method is required both for the standardization of tuberculin and for the clinical assessment of the tuberculin reaction to which standardized statistical procedures can be applied with consistent and reproducible results that can be reduced to a formula. The work to be reported in this paper was planned in an attempt to achieve these objectives.

[1] From the Research Laboratories, Parke, Davis and Company, Detroit, Michigan.

METHODS

White guinea pigs weighing between 375 and 400 Gm. were inoculated intraperitoneally with virulent *M. tuberculosis* following a procedure used routinely in this laboratory. Four to five weeks later, the skin on the back and sides of these animals was depilated by clipping and by rubbing with barium sulfide paste. Three or four graded doses of a tuberculin preparation (PPD) were injected in 0.1 ml. volumes intradermally on each side of the body. In case an unknown was compared with a standard, they were injected alternately on the same side. The dosages employed were those recommended for skin testing in humans.

The skin reaction was determined by measuring the diameter of the erythema evolved twenty-four and forty-eight hours following inoculation. The intensity of the reaction reached a maximum around twenty-four hours. When the reacting area was not exactly circular in shape, two diameters (maximum and minimum) were measured and the mean diameter was used in calculating the dose-response relationship.

In some experiments, the tuberculous pigs which had once been employed for skin testing were used again two to four weeks later. The results of this practice have been carefully checked and no tuberculin desensitization or lack of response has been found as long as the animals remained in sound physical condition.

RESULTS AND DISCUSSION

The data will be presented in two parts: (A) An analysis of the dose-response characteristics of the skin tuberculin reaction, and (B) an assay method for tuberculin preparations.

A. Skin Reaction to Dose of Tuberculin

The skin reaction to dose of tuberculin follows a linear relationship when the value of response (Y) and the dosage (X) are expressed in logarithms (figure 1).

$$\log Y = \log a + b \log X \qquad \text{Equation 1}$$

a, b = constants; or

$$Y = aX^b \qquad \text{Equation 2}$$

Obviously there is the same relationship whether the reaction is expressed by the diameter (D) of the erythema, its area—$\pi\left(\frac{D}{2}\right)^2$, its volume—$4/3\,\pi\left(\frac{D}{2}\right)^3$ or any other power of D (since $\log Y^c = C \log Y$).

The equation holds true for readings taken either at twenty-four or forty-eight hours after intradermal injection of tuberculin (figure 1). The twenty-four hour reading is favored, because the reaction is maximal at this time; furthermore, necrosis occurs at forty-eight hours with large doses of tuberculin.

Using area as a measure of response twenty-four hours after inoculation, and the value 20 for 0.00002 mg. of PPD, the equation 3

$$Y\,(D^2) = 17.0\,X^{0.349}$$

was found to fit the data in table 1. In deriving equation 3, there were 360 determinations (4 from each pig) which were obtained in 4 experiments (22 to 24 animals each). The estimates of the constants of equation 3 thus represent those for a large population. In early calculations (as for equation 3), the diameters

of the erythema at right angles were multiplied to obtain the area. The average diameter was used in later computations. The difference in values, as obtained

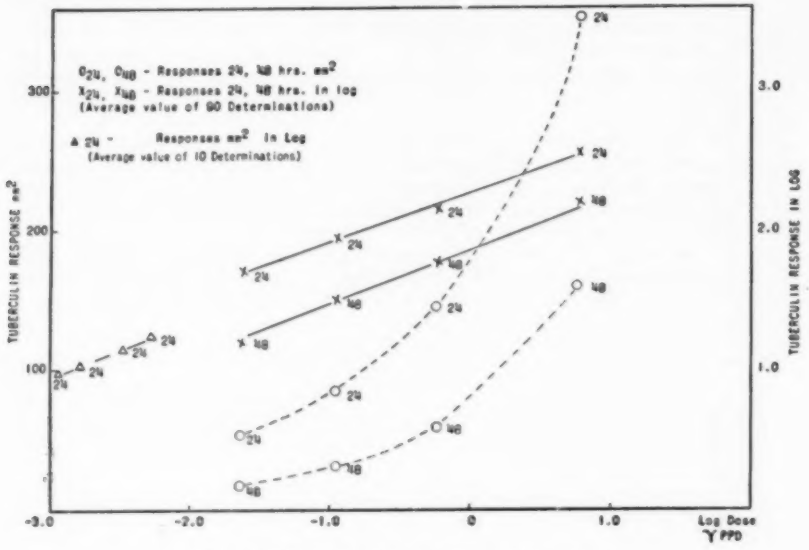

FIG. 1. Tuberculin dose-response relationships

TABLE 1

Tuberculin Skin Reaction

EXPERIMENT NUMBER	NUMBER OF PIGS	DOSE OF PPD/*SKIN REACTION IN MM.²							
		0.00002 mg.		0.0001 mg.		0.0005 mg.		0.005 mg.	
		24 hrs.	48 hrs.	24 hrs.	48 hrs.	24 hrs.	48 hrs.	24 hrs.	48 hrs.
1	22	64.9	23.2	97.0	31.5	154.7	61.7	418.8	174.7
2	22	51.1	19.9	89.9	40.5	152.2	64.4	351.2	187.1
3	22	46.6	15.5	81.3	30.2	141.7	53.7	333.6	137.5
4	24	38.4	8.1	62.6	20.0	115.0	46.4	301.2	136.4
Average value of 90 pigs.....		50.3	16.7	82.7	30.6	140.9	56.6	351.2	158.9

* = Average values of the number of guinea pigs in each experiment.

$$Y = 13.5\ X^{0.349},$$

Y = Skin reaction at 24 hours.
X = Dose of PPD (a value 20 for 0.00002 mg.)

in two ways, is very slight and is not significant statistically. The exponent 0.349, the slope of the regression line (equation 1), was computed by the method

of least squares. It has a standard error of ± 0.025. Equation 3 may therefore be written as

$$Y(D^3) = 17.0\, X^{1/3} \text{ or } Y(D) = \sqrt{17.0}\, X^{1/6}$$

In other words, a straight line may be obtained by plotting the response in mm^2 against the cubic root of the dosage of tuberculin or the response in diameter

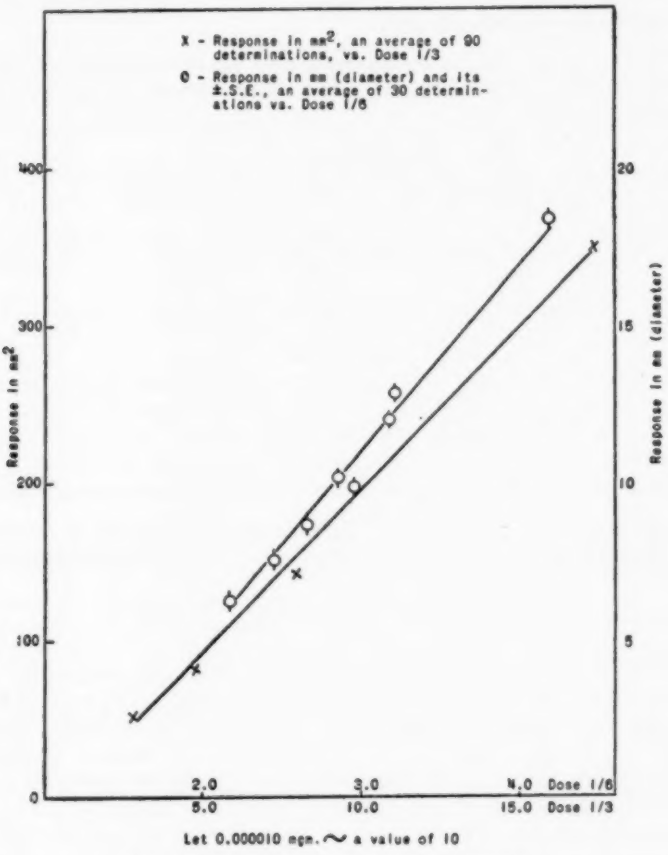

FIG. 2. Tuberculin dose-response relationship

against the 1/6 power of dosage. This is shown in figure 2. The two lines were drawn from data obtained in two separate experiments. One was plotted with the same data used to derive equation 3. The standard error of the mean indicates approximately the variation of the slope of the line. Fairly accurate estimation of slope may be obtained graphically with a much smaller number of

determinations as shown by graphs in figure 1. The question as to how many determinations are required in an accurate biological assay of tuberculin is discussed in the following section on assay method.

B. Assay of Tuberculin

From the dose-response relationship given above, an approximate estimation of the activity of an unknown tuberculin in reference to that of a standard tuberculin may be determined as follows:

Let X_{s1}, X_{s2}, X_u and Y_{s1}, Y_{s2} and Y_u be the doses and skin reactions in diameter (or area) of the erythema produced by the standard and the unknown tuberculin preparation respectively:

$$Y_{s1} = aX_{s1}^b, \qquad Y_{s2} = aX_{s2}^b, \qquad Y_u = aX_u^b$$

$$\frac{Y_{s2}}{Y_{s1}} = \frac{aX_{s2}^b}{aX_{s1}^b} = \left(\frac{X_{s2}}{X_{s1}}\right)^b, \qquad \text{or} \qquad \log\frac{Y_{s2}}{Y_{s1}} = b\log\frac{X_{s2}}{X_{s1}}$$

$$\text{When } \frac{X_{s2}}{X_{s1}} = 10, \qquad b = \log\frac{Y_{s2}}{Y_{s1}}$$

$$\text{If } X_{s1} = 1\gamma \text{ or } 1 \text{ mg.}, \qquad \log X_{s1} = 0$$

$$\log\frac{Y_u}{Y_{s1}} = b\log\frac{X_u}{X_{s1}} = \log\frac{Y_{s2}}{Y_{s1}}\cdot\log X_u$$

$$\log X_u = \frac{\log Y_u - \log Y_{s1}}{\log Y_{s2} - \log Y_{s1}}$$

In a special case, $\frac{X_{s2}}{X_{s1}} = 10$, $X_{s1} = 1$, and $b = 0.333$, when the reaction is measured in mm^2 as shown by equation 3, the activity of an unknown in reference to a standard is equal to the third power of the ratio of their tuberculin reactions

$$\log\frac{Y_u}{Y_{s1}} = b\log X_u, \qquad X_u = \left(\frac{Y_u}{Y_s}\right)^{\frac{1}{0.333}} = \left(\frac{Y_u}{Y_s}\right)^3$$

Quantitative assay procedure: The activity of a tuberculin preparation of unknown potency may be determined by experiments planned in factorial designs and evaluated through the analysis of variance. The statistical technique adopted here is that of Bliss, which has been used for the assay of penicillin and other drugs (9). The data obtained with a PPD preparation are given in table 2. Four concentrations were used, two designated as "standards" and the other two as "unknowns." The symbols in the table are self-explanatory. The relative potency of the unknown to the standard is obtained by a relative log-potency of $M = \frac{I\,T_1}{T_2}$, where I = logarithm of the ratio of the high dose to low dose for both standard and unknown, a required condition in the assay procedure. In some of the experiments, I was chosen by a ratio of $\log\frac{3.16}{1}$ or 0.5; above equa-

tion thus becomes

$$M = \frac{T_1}{2T_2}$$

The next step is to calculate the standard error of potency. An average standard error is

$$\text{S.E. of potency} = 2.30 \times Sm \times (\text{antilog } M), \text{ where}$$

$$Sm = \sqrt[\lambda]{\frac{1}{N}\left(1 + \frac{T_1^2}{T_2^2}\right)} \quad \text{and} \quad \lambda = \frac{S}{b}$$

(S = standard deviation of the population and b = slope of the regression line)

$$S = \sqrt{\frac{\Sigma(Y^2) - (T_1^2 + T_2^2 + T_3^2)/N}{12(N-1)}}$$

($\Sigma(Y^2)$ = sum of Y^2S and N = the number of tests in the assay). The slope is calculated by

$$b = \frac{T_2}{2IN}, \qquad b = \frac{T_2}{N} \text{ when } I = 0.5$$

The accuracy of the method is shown by the figures computed from the data of 3 experiments in tables 2 and 3.

The "unknowns" have assayed potencies 148.0 ± 11.95, 181.7 ± 20.0 and 142.7 ± 12.75 per cent that of the standard, while the actual potencies are 150, 200 and 150 per cent, respectively.

As indicated by the dose-response curve in figure 1, along a limited range, the response is approximately linear to the log-dose. Therefore, within this range, the above method may be used by a response-log dose relationship (instead of log-response and log-dose). As may be seen by comparing the values in table 2, there is no gain in the sensitivity of the method by using ordinary numbers instead of logarithms. The use of logarithms for responses has the advantage in that the linear relationship covers the entire range of doses.

Regarding the design of the experiment, the following conditions are suggested for a simple, rapid, and accurate procedure for the assay of tuberculin preparations.

Reactivity: As in any biological assay, the sensitivity and accuracy of a method depend upon both the reactivity and the uniformity in response of the testing animals. In tuberculin assays, therefore, only good reactors should be used. This requirement may usually be fulfilled by using "sound" guinea pigs in which a high degree of tuberculin sensitivity has been established.

Number of determinations: Ten determinations for each concentration, or 40 determinations for each assay, are appropriate numbers required. Forty determinations may be carried out in 5 pigs, by inoculating 4 doses in each side of the dorsal skin.

Dosage: Large doses, but under the necrotizing level at twenty-four hours after inoculation, should be used. The larger the erythema, the less will be the error introduced in reading the skin reaction. One to five γ (0.001–0.005 mg.)

TABLE 2

Assay of Tuberculin (PPD)

(A) $^{*}U_2$, U_1, S_2, S_1 = 4.74, 1.50, 3.16, 1.00 γ

TEST NUMBER	DIAMETER OF ERYTHEMA (LOG) FOR				$D_1 = U_2 - S_2$	$D_2 = U_1 - S_1$	$D_3 = U_2 - U_1$	$D_4 = S_2 - S_1$	$Y_1 = D_1 + D_3$	$Y_2 = D_2 + D_4$	$Y_3 = D_1 - D_3$
	$^{*}U_2$	U_1	S_2	S_1							
1	1.08	0.86	1.02	0.85	0.06	0.01	0.22	0.17	0.07	0.39	0.05
2	1.28	1.15	1.20	1.04	0.08	0.11	0.13	0.16	0.19	0.29	−0.03
3	1.22	1.00	1.11	0.98	0.11	0.02	0.22	0.13	0.13	0.35	0.09
4	1.23	1.10	1.18	1.06	0.05	0.04	0.13	0.12	0.09	0.25	0.01
5	1.16	1.06	1.13	1.00	0.03	0.06	0.10	0.13	0.09	0.23	−0.03
6	1.28	1.13	1.20	1.04	0.08	0.09	0.15	0.16	0.17	0.31	−0.01
7	1.31	0.98	1.23	0.90	0.08	0.08	0.33	0.33	0.16	0.66	0.00
8	1.18	1.02	1.13	0.93	0.05	0.09	0.16	0.20	0.14	0.36	−0.04
9	1.20	0.95	1.16	0.85	0.04	0.10	0.25	0.31	0.14	0.56	−0.06
10	1.18	1.02	1.15	0.95	0.03	0.07	0.16	0.20	0.10	0.36	−0.04
Total							1.28 = T_1		3.76 = T_3		−0.06 = T_5

M = 0.1702 or 148.0%; Actual = 150%.
b = 0.376, S = 0.0425, Sm = 0.03774, S.E. of Potency = 11.95%.

(B) $^{*}U_2$, U_1, S_2, S_1 = 4.74, 1.50, 3.16, 1.00 γ

TEST NUMBER	DIAMETER OF ERYTHEMA (LOG) FOR				$D_1 = U_2 - S_2$	$D_2 = U_1 - S_1$	$D_3 = U_2 - U_1$	$D_4 = S_2 - S_1$	$Y_1 = D_1 + D_3$	$Y_2 = D_2 + D_4$	$Y_3 = D_1 - D_3$
	$^{*}U_2$	U_1	S_2	S_1							
1	12.0	7.5	10.5	7.0	1.5	0.5	4.5	3.5	2.0	8.0	1.0
2	19.0	14.0	16.0	11.0	3.0	3.0	5.0	5.0	6.0	10.0	0.0
3	16.5	10.0	13.0	9.5	3.5	0.5	6.5	3.5	4.0	10.0	3.0
4	17.0	12.5	15.0	11.5	2.0	1.0	4.5	3.5	3.0	8.0	1.0
5	14.5	11.5	13.5	10.0	1.0	1.5	3.0	3.5	2.5	6.5	−0.5
6	19.0	13.5	16.0	11.0	3.0	2.5	5.5	5.0	5.5	11.5	0.5
7	20.5	9.5	17.0	8.0	3.5	1.5	11.0	9.0	5.0	20.0	2.0
8	15.0	10.5	13.5	8.5	1.5	2.0	4.5	5.0	3.5	9.5	−0.5
9	16.0	9.5	14.5	7.0	1.5	2.5	6.5	7.5	4.0	14.0	−1.0
10	15.0	10.5	14.0	9.0	1.0	1.5	4.5	5.0	2.5	9.5	−0.5
Total							38 = T_1		107 = T_3		5.0 = T_5

M = 0.1542 or 142.7%; Actual = 150%.
b = 10.70, S = 1.237, Sm = 0.03886, S.E. of Potency = 12.75%.

of PPD have been found to be satisfactory doses. The one γ (PPD) dose is chosen so that the units of tuberculin potency may be expressed, if desired, in simple terms of the weights of a standard.

For an "unknown" tuberculin preparation, its potency may be first estimated

approximately with one dose of the unknown and one dose of a standard, and calculated by the third power of the ratio of their skin reactions.

Measurement: The maximal skin reaction, twenty-four hours after inoculation, is favored for the evaluation of tuberculin preparations. It is immaterial whether the reaction is measured by the area or by the diameter of the erythema. For time saving in calculations, the diameter is preferred.

TABLE 3

Assay of Tuberculin (PPD)

(A)

TEST NUMBER	DIAMETER OF ERYTHEMA (LOG) FOR			
	*U_3	U_1	S_2	S_1
1	1.04	0.85	0.95	0.88
2	1.15	0.81	1.02	0.70
3	1.15	1.00	1.10	0.93
4	1.11	0.88	0.98	0.88
5	1.08	0.78	0.98	0.74
Total	$T_1 = 0.69$, $T_2 = 2.09$, $T_3 = 0.31$			

M = 0.230, or 170%; Actual 200%
b = 0.299, S = 0.0566, Sm = 0.092
S.E. of Potency = 35.97%

(B)

TEST NUMBER	DIAMETER OF ERYTHEMA (LOG) FOR			
	*U_3	U_1	S_2	S_1
1	1.04	0.85	0.95	0.88
2	1.15	0.81	1.02	0.70
3	1.15	1.00	1.10	0.93
4	1.11	0.88	0.98	0.88
5	1.08	0.78	0.98	0.74
6	1.06	0.78	0.88	0.74
7	1.10	0.85	1.02	0.78
8	1.13	0.88	1.02	0.85
9	1.08	0.88	1.04	0.74
10	1.16	0.90	1.04	0.74
Total	$T_1 = 1.66$, $T_2 = 4.48$, $T_3 = 0.40$			

M = 0.259 or 181.7%; Actual 200%
b = 0.320, S = 0.0469, Sm = 0.048
S.E. of Potency = 20.0%

*U_3, U_1, S_2, S_1 = 1, 0.2, 0.5, 0.1 γ of PPD.

SUMMARY

An analysis of the dose-response characteristics of the skin tuberculin reaction has been presented. Expressed in logarithms, the dose and the size of the erythema follow a linear relationship. The response, in terms of the area of the skin reaction, is proportional to the cubic root of the dose of tuberculin.

Based upon the lineality between dose and response, a statistical procedure has been used for the assay of tuberculin preparations. The relative potency of an unknown is computed from the regression line of a standard preparation. The relative potency is determined in experiments planned in factorial design and evaluated through the analysis of variance.

SUMARIO

La Cutirreacción a la Tuberculina para la Valoración de la Tuberculina en los Cobayos

Preséntanse un análisis de las características de la dosis-respuesta de la cutituberculinorreacción. Expresada en logaritmos, la dosis y el tamaño del

eritema mantienen una relación lineal. La respuesta, en términos del área de la cutirreacción, es proporcional a la raíz cúbica de la dosis de tuberculina.

Basándose en la alineación entre dosis y respuesta, se empleó un procedimiento estadístico para la valoración de las preparaciones de tuberculina. La potencia de una incógnita se computa por la línea de regresión de una preparación tipo. La potencia relativa es determinada en experimentos trazados en términos factoriales y valuados por el análisis de la variación.

Acknowledgment

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INHIBITION OF THE TUBERCULIN TYPE REACTION BY ANTIHISTAMINIC DRUGS AND RUTIN[1]

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INTRODUCTION

Since the outstanding elementary experiment of Robert Koch on the reinoculation of tubercle bacilli into the skin of the laboratory animal, much work has been expended on tuberculin sensitivity.

Sensitivity in general has been divided into two groups, humoral and cellular. In the humoral group the circulating antibodies are present in the intercellular fluid and blood stream. In this type of sensitivity the skin responds to intracutaneous injections of offending antigens with an immediate whealing reaction, as, for example, in ragweed hay fever. In the cellular group, the antibodies are present in the cells themselves and the skin responds with a delayed inflammatory reaction. This is the group to which the tuberculin type of sensitivity belongs.

Two well-known methods are used to test for delayed tuberculin sensitivity. The first is the contact or patch test method. When tuberculin is brought in contact with the sensitive skin, a reaction occurs in the epidermis within forty-eight hours with the development of spongiosis and intradermal vesiculation. The second type is the method of the intradermal injection of tuberculin. A reaction develops in the sensitive cutis in forty-eight hours with lymphocytic and epithelioid infiltration and a connective and vascular tissue response.

With the recent development of the antihistaminic drugs, more interest has been displayed in Lewis's histamine theory of sensitivity. It is believed that in the humoral group the union of antigen and antibody causes the release of histamine or a histamine-like substance which gives an immediate reaction. Antihistaminic drugs will inhibit this reaction (1, 2, 3). Histamine, according to present concepts plays no part in the delayed cellular reaction. Inference has been made, therefore, that the antihistaminic drugs have no influence on tuberculin sensitivity. If they do, it would be by some other mechanism.

In order to test further the validity of these theoretical considerations, an attempt has been made to inhibit the tuberculin type of reaction by means of antihistaminic agents and rutin.

METHODS

Old Tuberculin, Tuberculin, Purified Protein Derivative (PPD)[2], the Tuberculin Patch Test (Vollmer)[3], rutin[4], and pyribenzamine hydrochloride[5], in tablet and powder form were used in the following experiments.

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[1] From the Department of Medicine, Section of Allergy, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

[2] Parke, Davis & Co.,

[3] Lederle Laboratories.

[4] Generously supplied by E. R. Squibb & Sons, New York, N. Y.

[5] Generously supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Dilutions of Old Tuberculin were made in sterile buffered saline with the same vial of Old Tuberculin. All solutions were freshly prepared before administration, using sterile buffered saline as the diluent unless otherwise stated.

All tests were performed in corresponding sites of the flexor surfaces of the forearm, generally in the middle third. An ordinary 1.0 cc. tuberculin syringe and 25 gauge hypodermic needle were used and all injections were performed and results read by the same observer.

RESULTS

Oral Pyribenzamine and the Tuberculin Test

A group of 29 patients not receiving medication were injected intradermally with 0.1 cc. of Old Tuberculin in a dilution of 1:10,000. Reactions were observed in forty-eight hours, the diameters of swelling and erythema measured and traced on onion skin paper. One week later, these patients began oral administration of pyribenzamine in a dosage of 400 mg. daily in 4 equally divided doses. One hour after the second dose on the second day, when a total of 600 mg. of pyribenzamine had been consumed, the patients were reinjected in the opposite forearm with the same dose of Old Tuberculin. In forty-eight hours, after administration of 1,400 mg. of the drug, reactions were again observed, measured, traced, and compared with the original reactions. The diameter of swelling and erythema was used as the basis for comparison.

Ten patients had identical reactions in both tests, while 4 showed a smaller, and 15 a greater, reaction during administration of pyribenzamine.

Intradermal Pyribenzamine and the Tuberculin Test

One-tenth cc. of 1 per cent pyribenzamine was injected intradermally to produce a small wheal. No subjective symptoms resulted from the injection of pyribenzamine in any case. When the swelling had receded in about ninety to one hundred and twenty minutes, the identical site was injected with 0.1 cc. of 1:1,000 Old Tuberculin. For a control an injection of 0.1 cc. of 1:1,000 Old Tuberculin was administered in the opposite arm. Readings were made in forty-eight hours and compared. Of 5 patients, 4 had a lesser reaction in the site previously injected with pyribenzamine, and one greater, as compared to the controls.

A series of patients previously tested with 1:10,000 Old Tuberculin were given 0.1 cc. of 1 per cent pyribenzamine intradermally as in the previous experiment and were then injected with 0.1 cc. of 1:10,000 Old Tuberculin in the same site in two and one-half to three hours when the swelling subsided. In forty-eight hours the reactions were observed, measured, and compared with previous reaction. Four patients reacted to the same degree, 3 less and 3 more severely following injection of pyribenzamine than when the drug was not present in the skin.

Intradermal Pyribenzamine and the Tuberculin Patch Test

In 11 patients, 0.1 cc. of 1 per cent pyribenzamine was injected in each of two areas on the forearm, so spaced that the tuberculin-impregnated sites of the tuber-

culin patches could be applied directly thereon. Control patch tests were placed on the opposite arm. Strips were removed in forty-eight hours and readings were made at that time. All showed definite positive reactions on the control sites. Eight patients had identical reactions where pyribenzamine had been injected and 3 had a smaller reaction. Five patients were observed for forty-eight additional hours, but there was no change except for fading of all reactions at the time of the final reading.

Iontophoresis of Pyribenzamine and Tuberculin Testing

Pyribenzamine hydrochloride was introduced into an area of skin (3½ by 7½ cm.) of the forearm by means of a standard iontophoresis apparatus (4, 5) using one third milliampere per sq. cm. for five minutes and a 10 per cent solution of pyribenzamine hydrochloride. One hour later, when the primary erythema had subsided, the tuberculin patch was applied to this site. Control patches were applied to the opposite forearm. Both patches were removed in forty-eight hours. Readings and comparisons were made immediately, twenty-four and forty-eight hours later. Of the 4 patients thus tested, 3 reacted identically in all sites and one had a less severe reaction on the iontophorized site.

In another group of patients pyribenzamine was similarly introduced in an area of the forearm (3½ by 3¾ cm.) with the same apparatus, using one half milliampere per sq. cm. for five minutes. One hour later, with subsidence of erythema, the center of the infiltrated area was injected with 0.1 cc. of tuberculin (PPD) strength 1 or 2. A similar injection of PPD was simultaneously made in the opposite forearm. Reactions were measured in forty-eight and seventy-two hours. Of 5 patients given PPD strength 2, similar reactions in both arms occurred in 2, but 3 had more severe reactions in the arms infiltrated with pyribenzamine. One patient was given PPD strength 1, with identical reactions in both sites.

Simultaneous Injection of Tuberculin and Antihistaminic Agents Mixed in Vitro

PPD tablets, strength 1 or 2, were dissolved in 1 cc. of 1 per cent pyribenzamine. One-tenth cc. of this mixture was then injected intradermally in the forearm and 0.1 cc. of the control strength of PPD in sterile buffered saline was similarly injected in the opposite arm. Reactions were read in forty-eight hours. Six patients in whom strength 1 was used showed marked reduction in size of the reaction in the arm in which pyribenzamine and tuberculin were injected. Two of 3 patients given second strength PPD had a similar inhibition of the reaction.

In 2 patients in whom thephorin was used and in 2 with neohetramine instead of pyribenzamine, this mixture likewise gave smaller reactions than controls.

Histoplasmin and Pyribenzamine

One-tenth cc. concentrated histoplasmin was diluted with 9.9 cc. of 1 per cent pyribenzamine in normal saline and 0.1 cc. of the mixture was injected in the forearm. As a control 0.1 cc. of a mixture of histoplasmin in normal saline in a similar concentration was injected in the opposite forearm. Reactions were

observed in all in forty-eight hours. No differences were noted in either arm in 5 patients. One had slightly smaller reactions with the pyribenzamine and histoplasmin mixture.

Rutin and the Tuberculin Test

A group of 5 patients not receiving medication were injected intradermally with 0.1 cc. of Old Tuberculin in a dilution of 1:10,000. Reactions were observed in forty-eight hours, the diameters of swelling and erythema measured and traced on onion skin paper. One week later these patients began oral administration of rutin in a dosage of 160 mg. daily in 4 equally divided doses. On the first day, the patients received 80 mg. of rutin. One hour after the second dose on the second day, when 160 mg. had been consumed, the patients were again injected in the opposite forearm with the same dose of Old Tuberculin. Reactions were read in forty-eight hours, when 480 mg. of the drug had been administered, and were found to be identical with the original results.

Pyribenzamine and the Tuberculin Test in Guinea Pigs

Twelve guinea pigs weighing approximately 300 gm. were innoculated with tubercle bacilli from an actively growing culture. Six of the guinea pigs were given pyribenzamine orally in a dosage of 20 mg. per Kg. of body weight twice daily. The other 6 pigs were given no medication and were used as controls. On the ninth day all pigs were skin-tested on the abdomen with 1:1,000 Old Tuberculin. There was no reaction. On the twenty-fourth day, one control pig had a positve reaction and on the thirtieth day 3 control pigs were positive and one guinea pig receiving pyribenzamine gave a positive reaction. On the thirty-fifth day, 4 controls and one pyribenzamine guinea pig were positive. On the fortieth day one pig of each group died of tuberculosis. By the forty-third day, 4 controls and 2 pyribenzamine pigs were positive. One pig of each group died on the forty-eighth day, and two days later another pyribenzamine pig died. On the fifty-second day all tests were positive in the 4 controls and the 3 pyribenzamine pigs which still survived. The guinea pigs taking pyribenzamine appeared sleepy and lethargic throughout the experiment. In this small series, there appeared to be a slight delay in the development of tuberculin sensitivity in the guinea pigs receiving pyribenzamine. This may be due to a toxic reaction of the drug causing inhibition of the natural antibody formation.

DISCUSSION

Other workers previously have been unable to affect the tuberculin test using various antihistaminic drugs. Boquet (6) found that the early antihistaminic drugs given subcutaneously did not prevent guinea pigs from responding to tuberculin to which they have previously been sensitized. Breton (7) also was unable to prevent a positive Vollmer patch test by previously injecting 2,339 RP into the test site in a method similar to that used in the present experiments. Guy (8) was unable to inhibit the tuberculin reaction in 5 patients given pyribenzamine orally. However, the delayed eczematous type of reaction can be inhibited with pyribenzamine (9, 5).

In the present study it was not possible to influence the Mantoux test with high oral doses of pyribenzamine. Likewise, there appeared to be little effect on both the patch and intradermal tuberculin test when applied over sites previously infiltrated by injection or by iontophoresis with pyribenzamine.

Although statistically quite a few tests showed some inhibition, in most cases this inhibition was of small degree and probably within the normal variations of the test. Tuberculin reactions are notably inconstant. Of 22 patients tested on three occasions by Guy, only 5 showed rather constant results. Furthermore, Sulzberger states that in some cases repeated injections of tuberculin alter the sensitivity, in some increasing it and in others decreasing it. Rich has also observed variations in reactions to tuberculin tests. When tuberculin is mixed with any antihistaminic drug prior to testing, results are consistently diminished. This may be due to a chemical inactivation of the tuberculin by these drugs *in vitro*.

The histoplasmin skin test is comparable to the tuberculin test in that it also gives a delayed type of reaction. When mixed with pyribenzamine *in vitro* and injected, it failed to antagonize the reaction. Histoplasmin may not be affected by pyribenzamine *in vitro*.

It is believed that there is a relationship between capillary permeability and the delayed inflammatory tuberculin type of reaction. Rutin has been used to decrease capillary permeability. It has been shown (10) that rutin protects against anaphylactic shock. In the present study, however, it was not possible to prevent the tuberculin reaction by the oral administration of rutin.

CONCLUSION

The tuberculin type of sensitivity reaction is not affected by antihistaminic drugs or by rutin.

Pyribenzamine did not prevent the development of tuberculin sensitivity in guinea pigs infected with tubercle bacilli, although some delay in this development was noted.

The oral administration of rutin, another drug which has shown some antianaphylactic activity, failed to inhibit the tuberculin reaction.

CONCLUSIONES

Inhibición de la Reacción de Tipo Tuberculínico por Antihistamínicos y Rutina

La reacción de sensibilidad de tipo tuberculínico no es afectada por los antihistamínicos o por la rutina.

La piribenzamina no impidió la aparición de sensibilidad a la tuberculina en los cobayos infectados con bacilos tuberculosos, aunque se notó cierta tardanza en dicha aparición.

La administración oral de otra droga, la rutina, que ha mostrado alguna actividad antianafiláctica, tampoco inhibió la reacción a la tuberculina.

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EDITORIAL

Ten Beds per Death or Eradication, not Reduction, of Tuberculosis

Institutional isolation of tuberculosis has evolved as an incidental by-product of attempts to improve the condition of individual patients. The pioneers of the sanatorium movement, such as Brehmer and Trudeau, thought chiefly of the value of the sanatorium to the patients. But the value of segregation in diminishing the spread of the disease was suggested at a very early date. Koch himself, when announcing the communicability of this disease, advocated the control of tuberculosis through the suppression of the sources of infectious materials. In his classic book, *The Prevention of Tuberculosis*, Newsholme demonstrated, in 1908, that institutional segregation is the predominant factor in the decline of tuberculosis.

In the days when the tuberculosis death rate in the United States was around 200 per 100,000, there were only a few scattered sanatoriums, occupied to a great extent by what were then considered "favorable" cases for treatment. It then seemed visionary and impractical to ask that every patient with tuberculosis be institutionalized throughout the entire period of active disease, or even that patients should receive sanatorium care during the last year of their lives. But gradually, as facilities increased and tuberculosis decreased, the feasibility and desirability of such goals met with recognition.

In 1916 the Legislature of Massachusetts passed a law requiring hospitalization for tuberculosis equivalent to one bed per two annual deaths or one per 50,000 inhabitants (corresponding to a death rate of 100 per 100,000). In his admirable reports on the Framingham experiment a few years later, Armstrong recommended one bed per annual death. This was accepted by the National Tuberculosis Association and advocated for nearly a generation. By 1929 David Lyman recognized that a ratio of one bed for each annual death was too low. In his presidential address in 1940, Doctor H. D. Chadwick set a goal of two beds per death as the minimum requirement for the control of tuberculosis. Two years later, in *The Modern Attack on Tuberculosis*, Chadwick and Pope recommended at least two and one-half beds per annual death.

It was asserted then that States having as many as three beds per death were more than adequately supplied and would have no waiting lists and even some empty beds. As the tuberculosis death rate declined, however, the ratio of beds to deaths increased so that there is now an average of nearly three beds per death throughout the United States and in some communities more than six beds per death may be available and utilized. But this is still far below the ideal of sanatorium care for every patient affected with active tuberculosis throughout the period of infectivity.

Most tuberculosis workers, like Chadwick, have accepted the Framingham findings that approximately ten cases of active tuberculosis may be found in a community for each annual death. Whether really adequate institutional facilities for the total eradication of pulmonary tuberculosis will require five or twenty

beds per death, however, may vary in different communities, depending on the characteristics of the disease and other facilities available. In neglected groups with a high proportion of acute, rapidly progressive tuberculosis and poor facilities for treatment and consequent short duration of disease, as in the American Negro, Indian, and other special groups, the number of active cases which may be found by survey at any one time may be relatively small compared to the number expiring annually. On the other hand, in groups with sluggish, limited disease and abundant facilities for diagnosis and treatment, like World War I veterans, the duration of the disease may be greatly extended and many arrested, quiescent, and chronic cases may be discovered for each annual death.

There are now nearly 45,000 deaths annually in the United States from tuberculosis. About two-thirds of these, or 30,000 deaths a year, occur among the 120,000 beds in hospitals and sanatoriums. The majority of tuberculosis deaths in institutions, however, occur in general hospitals and other institutions which admit, for the most part, patients in advanced and preterminal conditions. About 14,000 deaths per annum occur in the 19,000 beds in special tuberculosis sanatoriums and hospitals, an intramural death rate of about 15 per cent per annum. Thus more than six beds per death are required to supply sanatorium care for the tuberculous patients of the kind who are at present in tuberculosis sanatoriums. It is notorious, however, that our tuberculosis hospitals and sanatoriums are overcrowded by patients with advanced disease. Ten beds for each annual death from tuberculosis would probably be required to provide institutional segregation for every patient with active tuberculosis in the United States.

The example of the American accomplishment in eradicating bovine tuberculosis within two decades of the initiation of an aggressive campaign against that disease points the direction in which we should go. Other countries, timorous and fearful of expense, have already wasted in condemned meat and low milk production far more than would have been necessary to eradicate the disease among their cattle.

Tuberculin tests and mass fluoroscopic and roentgenographic examinations of entire populations and intensive study of contacts of known cases of tuberculosis will reveal nearly all instances of active, "open" tuberculosis with cavity, the form responsible for most of the spread of the disease.

The increased rest made possible by increased bed capacity of sanatoriums and the newer methods of collapse therapy and chemotherapy have greatly improved the prognosis of these cases. A much greater proportion of patients may therefore be expected in the future to seek sanatorium treatment. Increased general education is needed as to the dangers of tuberculosis and the need for segregation. For those who fail to recognize the value to themselves and to their community of such institutional care and segregation, compulsory measures should be universally instituted just as they are today for other recognized communicable diseases.

It may not be feasible in all places to embark immediately upon an ambitious program for the provision of complete institutional care for all patients with active, communicable tuberculosis. But this can be recognized as our goal and any delay in putting it into execution must be understood to carry with it respon-

sibility for a definite number of deaths from tuberculosis which would be preventable if an all-out campaign for complete hospitalization and tuberculosis eradication were to be undertaken.

Before prematurely considering conversion of tuberculosis facilities and forces for combating other diseases, we should make sure that this condition has been really adequately handled. Patients with closed, arrested, and inactive disease, in whom repeated laboratory examinations fail to reveal discharge of tubercle bacilli, may be cared for in dispensaries, or offices, or in their homes. But any patient who is expectorating tubercle bacilli is a potential hazard to his community and under ideal conditions should certainly be segregated where danger of his spreading the disease may be averted. One bed per death was a grand slogan for 1918, ten beds per death or a bed for every patient with active tuberculosis should be our demand for 1950.

EMIL BOGEN

LETTERS TO THE EDITORS

PRECIPITIN TEST FOR CARBOHYDRATE ANTIBODIES IN HUMAN TUBERCULOSIS[1]

To the Editors of the American Review of Tuberculosis:

We wish to report that a precipitin test for carbohydrate antibodies in human tuberculosis has been obtained. The precipitating agent is the pure water soluble carbohydrate, which has been split by hydrolysis from the antigenic lipo-carbohydrate of the tubercle bacillus.

It has long been known that specific antibodies develop in humans and in experimental animals as a result of infection with the living tubercle bacillus, or through immunization with killed organisms.

From each of the fundamental constituents of the tubercle bacillus (proteins, lipids, carbohydrates), fractions have been isolated which have the property of reacting specifically (some tuberculo-carbohydrates to a high degree) with antibodies which are formed subsequent to infection, or to immunization with the killed organisms. Among these fractions, first the protein and then the lipid components were shown to be actively antigenic in inducing antibody formation when injected into normal animals. However, it has been found that these antigenic components have no power to promote the development of acquired resistance in experimental animals.

Three years ago we showed that the lipo-carbohydrate, extracted from a paraffin oil extract of the tubercle bacillus, is antigenic (Science, 1947, *105*, No. 2715). Preliminary observations in animals have indicated that this *antigenic* lipo-carbohydrate (the only one thus far extracted from the tubercle bacillus) does play a part in the mechanism of acquired resistance.

If antibodies play a part in the process of resistance to infection in human tuberculosis, one should not only be able to detect them in the circulating blood, but also to find some correlation between their presence or absence in the sera of tuberculous patients, and the resistance of these patients to infection, as observed clinically.

We were able to detect these antibodies in sera of tuberculous patients by a direct precipitin test, using as precipitating agent the pure carbohydrate (haptene) which was obtained, by hydrolysis, from our antigenic lipo-carbohydrate. As previously reported, this haptene gives precipitation in dilutions as high as one to ten million, with whole sera of some immunized rabbits (Am. Rev. Tubere., 1947, *56*, 222).

We did not attempt to make any quantitative determination of the titer of antibodies in the human sera of tuberculous cases, either by diluting the sera or by using the precise quantitative method developed by Dr. M. Heidelberger. Thus, our results have only a qualitative value.

Technique of the precipitin test: To perform the test, venous blood from human beings was collected in vacuum tubes, allowed to clot at room temperature, then stored at 4°C. overnight. Serum was removed after centrifugation at 2,000 r.p.m. for fifteen minutes, then recentrifuged at 4,500 r.p.m. for five minutes. Two cc. of sera were put in each of two sterile Wassermann tubes. To one of these tubes antigen was added, the other tube was kept as a control. The amount of antigen necessary to bring about a satisfactory

[1] This study was carried out under a grant from the Josiah Macy Foundation.

precipitation in a positive serum was found to be 5γ of the soluble carbohydrate, *i.e.*, one-twentieth of a cc. of 0.1 mg. per cc. solution. The tested sera as well as the control sera were stored at 4°C. for eight to ten days, and the readings were made after centrifugation for five minutes at 4,500 r.p.m. In a positive serum, a firm transparent disc is usually formed, which is easily seen by slight agitation of the tube. A false precipitate is sometimes found in both tubes, but these rapidly go into solution after some agitation.

Results: Two hundred ninety-eight sera from cases of tuberculosis have been tested thus far through the collaboration of Dr. A. Chaves. The classification of the state of the disease for all cases was made by Doctor Chaves. The specimens were obtained from various Health Department clinics and several hospitals. Two hundred nine of the 298 specimens were obtained from cases of active tuberculosis, comprising all varieties of the disease from rapidly progressive cases to regressive cases. Eighty-nine were inactive cases, classified according to whether the disease had been present for less or for more than two years. A table of the results obtained in the various groups is presented. The total in each group is small, but the trend of the results is interesting.

	TUBERCULOUS CASES					NORMAL AND OTHERS
	Active			Inactive		
	Rapidly progressive	Intermediate	Regressive	0 to 2 years	Over 2 years	
+	23	36	37	22	5	5
−	50	39	24	17	45	94
Number	73	75	61	39	50	99

It will be noted that antibodies were not found in the blood of all the active cases. Only in about 50 per cent of the active cases were the sera found to be positive. Nevertheless, the relative proportion of the positive to the negative sera was three times higher in the regressive cases (column 3) than in the rapidly progressive cases (column 1). An almost equal number of positive and negative sera was found in the intermediate group.

Antibodies were found in some of the inactive cases, but the relative proportion of positive to negative sera is very much higher in the infections which had been inactive for less than two years than in those inactive for more than two years.

As a control for the specificity of this precipitin test, the sera of 99 persons who presumably did not have tuberculosis were examined. Included in this group were specimens obtained from 47 normal persons, 5 patients with syphilis plus a pool of sera from 10 other early syphilitic infections, 13 patients with pneumonia, 15 with cancer, and 18 who had various other illnesses. Five positive reactions were found in this group of 99 individuals. One person was a contact of a case of active tuberculosis, 2 had recently recovered from a nontuberculous pneumonia, and 2 were patients in the chest clinic who were classified as "normal." The diagnosis of "nontuberculous" was made only on the basis of the chest roentgenogram.

These results seem to indicate that carbohydrate antibodies are more prevalent in tuberculous patients who are successfully fighting against the disease than in patients in which the infection is progressing rapidly. The results also show that antibodies remain present for a certain period of time in the sera of patients who have overcome the disease (from the clinical point of view).

This preliminary exploration suggests a possible correlation between these carbohydrate antibodies and the acquired resistance to the tuberculous infection. Quantitative serial determinations of the titer of antibodies in selected cases are needed before a conclusion can be reached concerning the protective power of these carbohydrate antibodies in human tuberculosis. The fact remains that a specific precipitin test is, for the first time, available in this disease.

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March 26, 1949.

BOOKS

Tuberculosis in the British Zone of Germany, with a Section on Berlin. Report of an Inquiry Made in September-October 1947 by M. Daniels, M.D., D.P.H., and P. D'Arcy Hart, M.D., F.R.C.P., Members of the Scientific Staff Medical Research Council. Pp. 32, His Majesty's Stationery Office, London, 1948, paper, Sixpence net.

Report on Tuberculosis in Germany (U. S. Zone) by a Commission Appointed by the Secretary of the Army, Composed of Esmond R. Long, M.D., Philip E. Sartwell, M.D., Colonel Silas B. Hays, M.D., and Major Alonzo W. Clark, M.S.C., March 5, 1948. Pp. 37.

Under government auspices both Great Britain and the United States have made surveys in occupied Germany for the purpose of determining the influence of World War II on the incidence, course, and death rate of tuberculosis during the War and its subsequent course and prevalence. The writers of these reports also discuss discovery, reporting, prevention, and management at the present time and present a discussion of manifest trends.

The assignment of the British investigation arose through a request from the Public Health Adviser addressed to the British Military Governor. As a result, the Ministry of Health was invited by the Foreign Office to arrange the investigation. The investigations were carried on in September and October, 1947, and reported in 1948. The main assignment was to the British Zone of Germany but attention was also directed to the situation in Berlin.

The survey conducted by the United States was initiated by orders from the Secretary of the Army, dated February 9, 1948. The members of the United States commission were directed "to investigate the incidence of, and recommend control measures for, tuberculosis among the German civilian population." The investigations were carried out and reported under date of March 5, 1948. This survey was limited to "Berlin and the three largest Länder of the U. S. Zone."

The British and the U. S. teams devoted approximately the same length of time to the respective surveys. Though not identically stated, their objectives were virtually the same, the problems confronting them were almost identical, their methods of approach were similar, and their findings were so nearly parallel as to inspire added confidence in their findings. In this brief review of the two reports, we can mention only their principal findings in relation to the effects of war and postwar trends.

Both surveys show the upsurge in the mortality rates as the War progressed, reaching its peak in 1945 and gradually declining since the War. On the whole, the rise in mortality was decidedly greater in urban than in rural communities and the larger the city, the sharper the rise. It is thought particularly by the U. S. commission that bombing, destruction of homes, the interruption of communications, and the resulting nervous strain plus a shortage of food supplies were important contributing factors. The British report indicates that in Berlin the death rate from all forms of tuberculosis was 90 in 1937 and 291 in 1945 (the peak). The United States study arrived at virtually identical conclusions. Both reports indicate that local health authorities through case finding and reporting are of the opinion that the incidence of active tuberculosis is increasing but the reporters believe this is a consequence of revival of the clinical services and case finding facilities and improved methods of diagnosis and discovery.

There is uniformity of opinion concerning the relatively high bed capacity for the management of tuberculous cases except in the city of Berlin. The situation in the British

Zone is decidedly better than in Great Britain. Compared on the basis of the usual ratio of beds to annual tuberculosis deaths, the report shows 2.2 in the British Zone as compared to 1.3 in England and Wales. In the U. S. Zone, approximately 2,000 beds are needed to bring the ratio up to two beds per annual tuberculosis death and 8,800 beds would be required in Berlin to meet this standard. The British report discusses mass roentgenographic findings which seem not to be particularly out of line with such surveys in England and America. The United States report mentions the employment of BCG and approved its employment provided it did not lessen the emphasis on other methods of control. It is agreed that in both the British and the U. S. Zones there seems to be a moderate postwar increase in the nonpulmonary forms of tuberculosis and that this may be attributed to the high incidence of tuberculosis among the dairy herds and imperfect methods of pasteurization of the milk.

Both reports are well supplied with tables and charts. The U. S. report covers World War I, thus posing interesting questions and permitting valuable comparisons. According to the United States report, the immediate effects and the ultimate course seem to run virtually parallel in the two World Wars and the figures confront us with a sharp warning against World War III.

In the opinion of the reviewer, these reports clearly show the evil effects of the stress and strain of war, both psychic and somatic, including disturbed nutrition, destruction of normal habitations, and the resulting displacements. These reports merit a careful study by all who are interested in tuberculosis.

LEWIS J. MOORMAN

WILLIAM B. TOLLEN: *Irregular Discharge: The Problem of Hospitalization of the Tuberculous, with a Foreword by Paul B. Magnuson and a Preface by John B. Barnwell. Veterans Administration, Washington, D. C., 1948. 64 pp. pamphlet, available from the Superintendent of Documents, Washington, D. C.*

The Veterans Administration operates, among other things, the largest single hospital system in the world for the treatment of tuberculous patients. It should provide a peculiarly favorable laboratory for the study of some of the unsolved problems in the control of this disease and the treatment of such patients. To some degree its tuberculous patients are a selected group in that they are predominantly males and that at some time they have been selected for military service. The net result, however, is a patient group far more homogeneous than any group of similar number which has been studied or may be studied in terms of behavior and its bearing on recovery. Mr. Tollen has utilized this unique laboratory to study irregular discharge which is a generic term for the inability or unwillingness of patients to complete medically indicated hospitalization.

As the author points out, veterans' hospitals enjoy no monopoly of this problem. The literature on this subject from which he cites, while scanty in quantity, is sufficient to indicate that the rejection and premature termination of prescribed treatment seriously limits many preventive and therapeutic efforts. It would appear that isolation can aid tuberculosis control only when it consistently and successfully isolates a substantial proportion of infective patients. In many resistant groups, younger adult males are often conspicuous among the problem cases.

In a number of previous studies the data, as above suggested, are sometimes incompletely homogeneous. Some of them are colored by the a priori convictions of the authors who, in some instances, have been a party to such conflicts over long periods of time.

Often these writers' knowledge of the disease has seemed far superior to their grasp of the intricacies of human behavior.

Possibly as a result of reviewing such studies in advance of this study, a fresh approach and technique have been utilized. Experienced social workers, to whom the assignment was a new task and not an ancient frustration, were assigned to interview veterans whose discharge had been irregular. The sample selected was the accessible portion of all irregularly discharged patients who left treatment facilities during July, 1947. The hospitals were operated or financed by the Veterans Administration. The number of patients interviewed was 401.

This procedure yielded some figures which have been presented in appropriately simple tables. In this study they are used to check and validate qualitative observation and experience rather than as an isolated source for conclusions. The selection of a single time interval eliminates variations due to changing economic and seasonal factors. The author has carried on concurrently a thoughtful examination of medical and psychological literature dealing with the behavior of patients and others in comparable circumstances. Accordingly, this reviewer is perplexed that Mr. Tollen appears to remain unaware of the degree to which chronic patients other than the tuberculous also resist medical intentions and advice. The problem of infection has brought such behavior into the spotlight in tuberculosis. Are we to believe that the death toll from coronary thrombosis, for example, includes no persons who have turned their backs on sound medical advice? Or are we dealing with a common human pattern of behavior which the presence of tuberculosis throws into high relief?

In this report we have presented to us the statements of the patients regarding their motivation and evaluation by trained interviewers, who also had access to hospital records. Whether or not one agrees wholly with such evaluation, it is apparent that the study is an effort to ascertain the facts and not an attempt to justify (or to discredit) medical or administrative method. The willingness of the Veterans Administration to review its effectiveness in this way is a reassuring attitude. The efforts of medical personnel to supplement its own perspectives by those of other disciplines also augurs well for the future development of the VA Tuberculosis Service.

The author's conclusions, which he presents with considerable eloquence, are far from arbitrary. He offers no single panacea. On two points his conclusions resemble those of Betty MacDonald (author of *The Plague and I*, a lay study of how tuberculosis treatment looked to a patient), first that recovery from tuberculosis may depend considerably upon the degree of self-discipline achieved by the patient and, second, that the confidence of the patient in the persons who order and administer his treatment may be a key to that discipline. Both authors reject the notion that everything beside the lesion may be dumped into the lap of some extra-medical worker and dismissed, no matter what skills are involved. Both see the most complete supplemental staffing of a hospital as but the lengthened shadow of the physician and his understanding of the patient's problems of treatment and recovery.

It is to be hoped that this pamphlet is only the first installment in a habitual and continuing study of the behavior of tuberculous veterans and its relation to their treatment and recovery. This publication is unimpeded by professional jargon or official gobbledegook. It provides food for thought both for those who are concerned with veterans' affairs and for those who wish to make isolation and treatment of the tuberculous a more effective instrument in the control of the disease.

HOLLAND HUDSON

H. BURNAND, H. JAEGER, M. AMSLER, F. VERREY, E. MARTIN, J. L. NICOD, P. HARDUROY: *Le Problem des Tuberculoses Atypiques. Pp. 429 with 39 illustrations, Masson et Cie., Paris; F. Roth et Cie., Lausanne, 1946, Paper.*

This volume is not merely a discussion of unusual forms of disease known to be caused by the tubercle bacillus. It also treats of conditions which have only been suspected of such an origin. The problem of determining from analogy and deduction, with a reasonable degree of probability, the tuberculous nature of an affection, without demonstrating the actual presence of the Koch bacillus in its lesions, is a difficult one. In this work, seven Swiss scientists from the universities of Lausanne and Zurich and from Geneva have attacked it valiantly and comprehensively. Their avowed purpose has been to assemble in a manual the current ideas about undeveloped and latent tuberculosis with such clinical, histological, and bacteriological evidence as is available to support them. That they have been able to produce and publish so readable and useful a volume so soon after the war is to their credit. This reviewer does not know of any similar work in English.

In their clinical studies they have investigated atypical tuberculoid conditions in the lung, including labile pulmonary infiltrates such as are seen in epituberculosis, in Löffler's syndrome, in certain cases of asthma in bronchiectasis, in a condition they designate as "debility of the bronchial mucosa" and in Boeck's sarcoid. An entire chapter is devoted to conditions attributed to the action of toxins derived from a tuberculous focus, possibly remote or concealed. Such conditions are often diagnosed as due to constitutional inadequacy. The authors consider them to be the result of a state of chronic infection or of latent tuberculosis. Such conditions are perhaps more readily attributed to tuberculosis in Europe than they would be in localities in America where tuberculosis is less prevalent.

Dermatological and ocular conditions suspected of having a tuberculous origin are fully discussed as is "tuberculous rheumatism" of which so much is written in French and so little in English.

Nicod in his summary of the histological studies speaks of early nonspecific changes due to tuberculosis which never reach the stage of tubercle formation but remain simple inflammatory reactions. On the other hand, typical tuberculous processes, such as caseation or calcification, may eventually disappear in healed or latent tuberculosis and be replaced by fibroid or cicatricial lesions. Harduroy, the bacteriologist, discusses atypical forms of the tubercle bacillus. Burnand sums up the results of all these studies in a paragraph of "final considerations" instead of "conclusions." Identification of acid-fast tubercle bacilli, he says, can no longer be considered the sole criterion of atypical tuberculosis. While we wait for new laboratory techniques, lacking today, there are certain morbid states that can be recognized as tuberculous by their clinical manifestations. This is in line with the present trend of considering the inherited and acquired characteristics of the individual as prime factors in the development and course of his disease.

ARTHUR T. LAIRD

SELMAN A. WAKSMAN. *The Literature on Streptomycin 1944–1948. Pp. xv–112, 1948, Rutgers University Press, New Brunswick, New Jersey, cloth, $3.00.*

A bibliography of the world's literature on streptomycin is of great value to both clinicians and research workers. This small volume lists 1171 papers, monographs, and books dealing with every aspect of the subject. Another 40 references are given to work on the

Actinomyces, the production of antibiotic substances, and on streptothricin. The author index has cross references to all the authors of each paper and is very useful. The references on streptomycin, however, are listed roughly in the order of their appearance and are indexed only by the principal topic of each paper. This arrangement detracts considerably from the usefulness of the volume, especially for those who are not already familiar with much of the work on streptomycin. The important paper which appeared in 1944 announcing the isolation of streptomycin by A. Schatz, E. Bugie, and S. A. Waksman is reprinted in full.

LAWRENCE B. HOBSON

J. K. DONALDSON: *Surgical Disorders of the Chest. Second Edition. Pp. 485, Lea and Febiger, Philadelphia, 1947, cloth, $8.50.*

The main additions to the first edition of this work (1944) include a description of the advances made in traumatic thoracic surgery during World War II and more details in the treatment of pleurisy, surgical diseases of the esophagus, and the surgery of congenital cardiovascular anomalies.

In his preface, the author states that the volume is primarily designed as a reference book for physicians, surgeons, and medical students. He indicates that sufficient technical detail is included to permit the competent general surgeon to treat certain surgical disorders of the chest.

As the most recently published attempt to correlate what is new in the surgery of the chest, the book is certainly worthy of serious consideration and careful study. Many medical students and physicians, not specialists, will find it a useful reference text. The inclusion of the chapter on *Resuscitation and Inhalation Therapy* is a welcome addition to a surgical volume.

On the critical side several features of the book must be discussed. The over-all impression is that the text was written hurriedly. There are far too many references to other sections in the book, particularly following sections. This, combined with frequent parenthesized directions, makes for poor continuity both of text and thought. As a consequence either of carelessness in writing the original text or inadequate proof-reading, there are at least 40 examples of misspelled words, unwieldy English, and misquoted statistics.

Frontal roentgenograms are not positioned uniformly. On pages 132 and 310 they are reproduced differently in the same figure. On page 222 the roentgenogram is upside down. The roentgenographic illustrations frequently are inadequate, particularly the bronchograms. This may be due in part, however, to a poorer grade of paper in the second edition, undoubtedly necessary because of war restrictions.

In general, the illustrations are adequate and many are excellent. Figure 107 (page 324) is however, extremely small and is confusing even to a surgeon with considerable knowledge of hilar anatomy. Unfortunately, the colored plates on decortication lack third dimensional detail.

A few of the more obvious deficiencies in the text should be listed. The important role of endoscopic procedures in diagnosis and treatment is nowhere emphasized sufficiently. Specific examples are found in the inadequate discussion of indications for bronchoscopy in bronchiectasis, postoperative pulmonary complications, and tuberculosis. The inference is made throughout that the thoracic surgeon usually does not perform his own endoscopies, an entirely unwarranted impression.

On page 156, in discussing the treatment of tuberculous effusion and empyema (which this reviewer believes would preferably be discussed with tuberculosis) no mention is made of the status of the underlying lung as a factor in dictating either treatment or prognosis. On page 256, there is an inadequate discussion of pulmonary hilar and segmental anatomy. On page 291, only passing comment is made on carcinoma of the upper esophagus and there are no references in the bibliography to carcinoma in this location. The description of pulmonary cysts, emphysematous blebs and their differential diagnosis on page 306 is inadequate. There is insufficient separation of so-called bronchial adenoma from primary carcinoma of the lung (page 312). Specifically, there is no description of the microscopic pathology and no attempt at clinical differentiation. On page 361 *et seq.*, the collapse therapy of pulmonary tuberculosis is covered rather sketchily. I disagree with the expressed opinion that the objective of penumothorax therapy is complete collapse of the lung. Streptomycin therapy is not discussed at any length, but the section may have been completed too early for attempts at critical evaluation. There is no discussion of open pneumonolysis or of pneumoperitoneum. The section on extrapleural pneumothorax belongs in the chapter on extrapleural pneumonolysis. There should be greater elaboration of the role of lobectomy and pneumonectomy in the treatment of pulmonary tuberculosis.

Finally, a discussion and description of methods which are now obsolete add nothing to the practicability of a book designed primarily as a working manual for others than thoracic specialists. Only a few of these will be mentioned. "Emergency" pericostal suture for a bleeding intercostal vessel is a discarded technique. The use of an indwelling needle in the treatment of pressure (not tension) pneumothorax is not the best practice. There is no longer a necessity for stressing the avoidance of entering the pleural cavity in the surgical approach to cardiac wounds, or in pericardectomy. There is little or no object in describing an extrapleural approach to posterior mediastinal tumors. The text contains confusing allusions to tourniquet ligation in lobectomy and pneumonectomy. The inference that tourniquet ligation is *ever* indicated in pneumonectomy for carcinoma is challenged.

In conclusion, the rapid improvement of thoracic surgical techniques and the widened indications for operative interference in many thoracic diseases make it advisable that this material be assembled in available form. The author obviously has expended much effort in the preparation of the first and second editions. It is to be hoped that, if a third edition is contemplated, more care will be exercised in obtaining smoothness and clarity; that pertinent additions and deletions will result in a more useful compendium.

PAUL C. SAMSON

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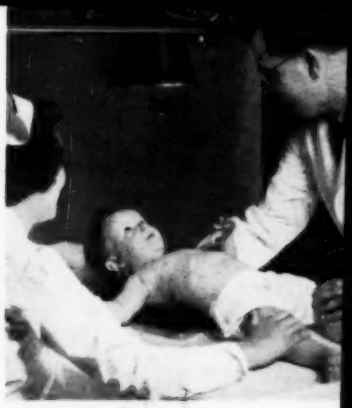

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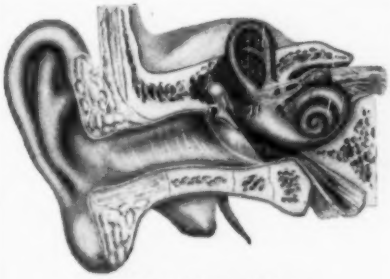

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PROTEIN	32 Gm.	VITAMIN B_1	1.16 mg.
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CARBOHYDRATE	65 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
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——*Dempsey, T. G. and Logg, M. H.:*
The Lancet, Dec. 13, 1947, p. 872.

*PARASAL is the trade name of PAS as distributed to the medical profession by the Panray Corp.

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